

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208700Orig1s000**

**OTHER REVIEW(S)**

**PMR/PMC DEVELOPMENT TEMPLATE**  
For 506B Reportable<sup>1</sup> PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

**Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”**

**Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>**

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**SECTION A: Administrative Information**

**NDA/BLA/Supplement #**            **NDA 208700**  
**PMR/PMC Set (####-#)**            **3326-02**  
**Product Name:**                    Lutathera (Lutetium Lu 177 Oxodotreotide)  
**Applicant Name:**                 Advanced Accelerator Applications USA, Inc. (AAA)  
**ODE/Division:**                    OHOP/DOP2

**SECTION B: PMR/PMC Information**

**1. PMR/PMC Description**

Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up from an adequate number of patients enrolled in clinical trials to identify and characterize the risks of myelodysplastic syndrome and acute leukemia with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

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<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

## 2. PMR/PMC Schedule Milestones<sup>2, 3</sup>

Section 2 is not applicable as no new studies are being requested.

Final Analysis Plan Submission:	June 2018
Interim Safety Report Submission:	September 2021
Final Report Submission:	December 2025

### SECTION C: PMR/PMC Rationale

#### 1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.

[Based on the mode of excretion of LUTATHERA, an increased risks of myelodysplastic syndrome and acute leukemia are suspected. An increased risk of myelodysplastic syndrome, a precursor of acute leukemia was reported in the NETTER-1 trial which supported the approval. However, the proposed follow-up time of 5 years following end of treatment for patients in the NETTER-1 trial is not sufficient to define the magnitude of the risk since onset of this event may not occur for up to 10 years following treatment. Additional follow-up time is required in a defined study population to more precisely estimate the risk and the time to onset of this serious adverse event.]

#### 2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

#### 3. For FDAAA PMRs and 506B PMCs only

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

**The study or trial can be conducted post-approval because: *[Select all that apply]***

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

4. **For FDAAA PMRs only *[for PMCs skip to Q.5]. Complete this entire section***

**a. The purpose of the study/clinical trial is to: *[Select one, then go to Q.4.b]***

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

***Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.***

**b. FAERS<sup>6</sup> and Sentinel's postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

***[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]***

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

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<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[The desired information needs to come from a clinical trial.]

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e ]***

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

The requested information can only be obtained from a clinical trial.

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**  
*[Select either “Yes” or “No” and provide the appropriate responses.]*

**Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

**No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f.  **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

*[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]*

**TYPE OF STUDY**

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study

### TYPE OF STUDY

Other (describe)

### TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)\*\*
- Thorough Q-T clinical trial
- Other (describe) Additional follow-up time is required in a defined study population to more precisely estimate the risk and the time to onset of this serious adverse event

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

#### **SECTION D: PMR/PMC Additional Information**

**1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

Yes

No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

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**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>**

1. **The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because:** *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2.  **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3.  **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Insert electronic signature (usually the Deputy Director for Safety)

## Appendix A PMR/PMC Development Template (FRM-ADMIN-60)

### Instructions for Use

[click [here](#) to return to the template]

#### ***Purpose:***

The PMR/PMC Development template (hereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

#### ***Who completes this template:***

The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

#### ***How to complete this template:***

The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B “reportable” PMC.<sup>10</sup> The separate templates are then combined into one document for archiving (see “How to archive the completed template”).

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

#### ***How to archive the completed template:***

The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B “reportable” PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.<sup>11</sup> This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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<sup>10</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

<sup>11</sup> A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

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**Instructions:**

**SECTION A: Administrative Information** [Click [here](#) to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

**SECTION B: PMR/PMC Information** [Click [here](#) to return to Section B of the template]

- 1. PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA’s PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant’s timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.<sup>12</sup>

Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., “Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*”). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a ‘standard’ PMR/PMC description may be employed [\[see Appendix B for examples\]](#).

- 2. PMR/PMC Milestones:** List the PMR/PMC milestones in the specified format.

Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered “core” PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.<sup>13</sup>

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<sup>12</sup> The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable.

<sup>13</sup> “Final” implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period

“Other” milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.<sup>14</sup>

### **SECTION C: PMR/PMC Rationale** [Click [here](#) to return to Section C of the template]

#### **1. Describe the review issue and the goal of the study or clinical trial.**

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

*DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.*

*DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.*

#### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.**

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

#### **3. For FDAAA PMRs and 506B PMCs only**

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needed to create a well-designed study or clinical trial. See FDA guidance for industry, [Postmarketing Studies and Clinical Trials — Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act](#).

<sup>14</sup> Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B “reportable” PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

#### 4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS<sup>15</sup> and Sentinel’s ARIA<sup>16</sup> system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

##### **Question 4.a: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

##### **Questions 4.b-d: Explanation of whether FAERS and Sentinel’s postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

##### **Question Q4.e: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

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<sup>15</sup> FDA Adverse Event Reporting System (FAERS)

<sup>16</sup> Active Risk Identification and Analysis (ARIA)

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

**Question Q4.f: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

**5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?**

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either “type of study” or “type of clinical trial.” Do not choose a option under both categories.

**SECTION D: PMR/PMC Additional information** [Click [here](#) to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

**1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?**

Select “yes” if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

**2. This study or clinical trial focuses on the following special population or circumstances:**

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select “not applicable.”

**3. (Complete if applicable) Additional comments about the PMR/PMC.**

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 “core” milestones).

Note: Additional milestones also must be tracked by the division (see [MAPP 6010.2](#), *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

**SECTION E: PMR/PMC Development Coordinator Statements** [Click [here](#) to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division’s Deputy Director for Safety) who will sign off on the completed Development Template.

**1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):**

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

**2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

**3. This PMR/PMC has been reviewed for clarity and consistency... reliability of drug quality.**

This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

## APPENDIX B

### Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

#### 1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment  
Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Hepatic Impairment  
Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)  
Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”
- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#  
Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

#### 2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy.

- Drug-Drug Interactions (gastric acid reducing agents)  
Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.
- Drug-Drug Interactions-Induction  
Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”
- Anti-Drug Antibody Responses  
Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient’s test sample at each sampling point.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUZANNE G DEMKO  
01/24/2018

JEFFERY L SUMMERS  
01/24/2018

**PMR/PMC DEVELOPMENT TEMPLATE**  
For 506B Reportable<sup>1</sup> PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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**SECTION A: Administrative Information**

**NDA/BLA/Supplement #**      **NDA 208700**  
**PMR/PMC Set (####-#)**      **3326-01**  
**Product Name:**              Lutathera (Lutetium Lu 177 Oxodotreotide)  
**Applicant Name:**            Advanced Accelerator Applications USA, Inc. (AAA)  
**ODE/Division:**              OHOP/DOP2

**SECTION B: PMR/PMC Information**

**1. PMR/PMC Description**

Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up from an adequate number of patients enrolled in clinical trials to identify and characterize the risk of renal failure with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

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**2. PMR/PMC Schedule Milestones<sup>2, 3</sup>**

<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

**Section 2 is not applicable as no new studies are being requested.**

Final Analysis Plan Submission:	June 2018
Interim Safety Report Submission:	September 2021
Final Report Submission:	December 2025

**SECTION C: PMR/PMC Rationale**

**1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.**

[Based on the mode of excretion of LUTATHERA, an increased risk of renal failure is suspected. An increased risk of renal toxicity was reported in the NETTER-1 trial which supported the approval. However, the proposed follow-up time of 5 years following end of treatment for patients in the NETTER-1 trial is not sufficient to define the magnitude of the risk since onset of this event may not occur for up to 10 years following treatment. Additional follow-up time is required in a defined study population to more precisely estimate the risk and the time to onset of this serious adverse event.]

**2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)**

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR:** Meets PREA postmarketing pediatric study requirements *[Skip to Q.5]*
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

**3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because: *[Select all that apply]***

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

4. **For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section**

a. **The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b ]**

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

**Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.**

b. **FAERS<sup>6</sup> and Sentinel’s postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

**[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d ]**

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

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<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[The desired information needs to come from clinical trial data.]

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e ]***

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[The information requested can only be derived from a clinical trial.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**  
*[Select either “Yes” or “No” and provide the appropriate responses.]*

**Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

**No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f.  **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

*[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]*

**TYPE OF STUDY**

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study

### TYPE OF STUDY

Other (describe)

### TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)\*\*
- Thorough Q-T clinical trial
- Other (describe) Additional follow-up time is required in a defined study population to more precisely estimate the risk and the time to onset of this serious adverse event

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

### SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

Yes

No

**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

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**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because:** *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2.  (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3.  **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Insert electronic signature (usually the Deputy Director for Safety)

## Appendix A PMR/PMC Development Template (FRM-ADMIN-60)

### Instructions for Use

[click [here](#) to return to the template]

#### ***Purpose:***

The PMR/PMC Development template (hereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

#### ***Who completes this template:***

The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

#### ***How to complete this template:***

The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B “reportable” PMC.<sup>10</sup> The separate templates are then combined into one document for archiving (see “How to archive the completed template”).

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

#### ***How to archive the completed template:***

The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B “reportable” PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.<sup>11</sup> This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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<sup>10</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

<sup>11</sup> A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

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**Instructions:**

**SECTION A: Administrative Information** [Click [here](#) to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

**SECTION B: PMR/PMC Information** [Click [here](#) to return to Section B of the template]

- 1. PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.<sup>12</sup>

Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed [\[see Appendix B for examples\]](#).

- 2. PMR/PMC Milestones:** List the PMR/PMC milestones in the specified format.

Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.<sup>13</sup>

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<sup>12</sup> The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable.

<sup>13</sup> "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period

“Other” milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.<sup>14</sup>

## **SECTION C: PMR/PMC Rationale** [Click [here](#) to return to Section C of the template]

### **1. Describe the review issue and the goal of the study or clinical trial.**

This section should summarize the **rationale** for the study/trial. The section should **not** repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

*DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.*

*DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.*

### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.**

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

### **3. For FDAAA PMRs and 506B PMCs only**

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needed to create a well-designed study or clinical trial. See FDA guidance for industry, [Postmarketing Studies and Clinical Trials — Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act](#).

<sup>14</sup> Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B “reportable” PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

#### 4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS<sup>15</sup> and Sentinel’s ARIA<sup>16</sup> system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

##### **Question 4.a: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

##### **Questions 4.b-d: Explanation of whether FAERS and Sentinel’s postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

##### **Question Q4.e: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

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<sup>15</sup> FDA Adverse Event Reporting System (FAERS)

<sup>16</sup> Active Risk Identification and Analysis (ARIA)

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

**Question Q4.f: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.**

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

**5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?**

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either “type of study” or “type of clinical trial.” Do not choose a option under both categories.

**SECTION D: PMR/PMC Additional information** [Click [here](#) to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

**1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?**

Select “yes” if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

**2. This study or clinical trial focuses on the following special population or circumstances:**

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select “not applicable.”

**3. (Complete if applicable) Additional comments about the PMR/PMC.**

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 “core” milestones).

Note: Additional milestones also must be tracked by the division (see [MAPP 6010.2](#), *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

**SECTION E: PMR/PMC Development Coordinator Statements** [Click [here](#) to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division’s Deputy Director for Safety) who will sign off on the completed Development Template.

**1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):**

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

**2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

**3. This PMR/PMC has been reviewed for clarity and consistency... reliability of drug quality.**

This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

## APPENDIX B

### Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

#### 1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment  
Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Hepatic Impairment  
Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)  
Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”
- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#  
Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

#### 2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy.

- Drug-Drug Interactions (gastric acid reducing agents)  
Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.
- Drug-Drug Interactions-Induction  
Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”
- Anti-Drug Antibody Responses  
Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient’s test sample at each sampling point.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUZANNE G DEMKO  
01/24/2018

JEFFERY L SUMMERS  
01/24/2018

**PMR/PMC DEVELOPMENT TEMPLATE**  
For 506B Reportable<sup>1</sup> PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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**SECTION A: Administrative Information**

NDA/BLA/Supplement #      **208700**  
PMR/PMC Set (####-#)      3326-3  
Product Name:              Lutathera  
Applicant Name:            Advanced Accelerator Applications  
ODE/Division:              OHOP/DOP2

**SECTION B: PMR/PMC Information**

**1. PMR/PMC Description**

Submit the final clinical report and datasets at the time of the final analysis for overall survival (OS) for Trial NETTER-1, entitled “A Multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate to Octreotide LAR in Patients with Inoperable, Progressive, Somatostin Receptor Positive, Midgut Carcinoid Tumors”, to revise product labeling with mature OS data.

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**2. PMR/PMC Schedule Milestones<sup>2, 3</sup>**

Final Report Submission:              May 2021

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<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

## SECTION C: PMR/PMC Rationale

### 1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.

To update labeling with mature OS data and to demonstrate that no decrement in OS is observed.

### 2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR: Meets PREA postmarketing pediatric study requirements *[Skip to Q.5]*
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- X PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

### 3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- X Longer-term data needed to further characterize the safety/efficacy of the drug
- X Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- X Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b ]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

*Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.*

b. **FAERS<sup>6</sup> and Sentinel's postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d ]*

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

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<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e ]***

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**  
*[Select either “Yes” or “No” and provide the appropriate responses.]*

- No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*
- Need to minimize bias and/or confounding via randomization
  - Need for placebo control
  - Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
  - Need pre-specified and prospective active data collection of the outcome/endpoint of interest
  - Other

*[If you selected “other,” expand on the reason(s) why a study is not sufficient.]*

f.  **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?

*[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]*

TYPE OF STUDY
<input type="checkbox"/> Drug interaction or bioavailability studies (nonclinical only)
<input type="checkbox"/> Epidemiologic (observational) study related to safe drug use
<input type="checkbox"/> Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
<input type="checkbox"/> Immunogenicity study (nonclinical)
<input type="checkbox"/> Meta-analysis or pooled analysis of previous observational studies
<input type="checkbox"/> Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
<input type="checkbox"/> Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
<input type="checkbox"/> Pharmacogenetic or pharmacogenomic study
<input type="checkbox"/> Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
<input type="checkbox"/> Quality CMC study (e.g., manufacturing, studies on impurities)
<input type="checkbox"/> Quality stability study
<input type="checkbox"/> Registry-based observational study

TYPE OF STUDY
<input type="checkbox"/> Other (describe) _____

TYPE OF CLINICAL TRIAL
<input type="checkbox"/> Combined PK/PD, safety and/or efficacy trial ( <i>PREA* PMRs only</i> ) <input type="checkbox"/> Dose-response clinical trial <input type="checkbox"/> Dosing trial (e.g., alternative dosing schedule) <input type="checkbox"/> Drug interaction or bioavailability clinical trial (clinical only) <input type="checkbox"/> Immunogenicity trial (clinical) <input type="checkbox"/> Meta-analysis or pooled analysis of previous clinical trials <input type="checkbox"/> Pharmacogenetic or pharmacogenomic clinical trial <input type="checkbox"/> Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial <input checked="" type="checkbox"/> Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints) <input type="checkbox"/> Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – <i>excludes SOT</i> <input type="checkbox"/> Safety outcomes trial (SOT)** <input type="checkbox"/> Thorough Q-T clinical trial <input type="checkbox"/> Other (describe) _____

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

**SECTION D: PMR/PMC Additional Information**

**1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- Yes
- No

**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- X Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

Because this is an ongoing trial and patients are being followed for safety, the only milestone of interest is the final OS analysis and report. No other milestones are relevant.

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**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because:** *[Select all that apply]*

- X The study/clinical trial meets criteria for a PMR or a PMC.
- X The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- X The applicant has adequately justified the choice of milestone dates.
- X The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2. X (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Insert electronic signature

## Appendix A PMR/PMC Development Template (FRM-ADMIN-60)

### Instructions for Use

[click [here](#) to return to the template]

#### ***Purpose:***

The PMR/PMC Development template (hereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

#### ***Who completes this template:***

The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

#### ***How to complete this template:***

The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B "reportable" PMC.<sup>10</sup> The separate templates are then combined into one document for archiving (see "How to archive the completed template").

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

#### ***How to archive the completed template:***

The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B "reportable" PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.<sup>11</sup> This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

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<sup>10</sup> 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

<sup>11</sup> A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

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## ***Instructions:***

### **SECTION A: Administrative Information** [Click [here](#) to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

### **SECTION B: PMR/PMC Information** [Click [here](#) to return to Section B of the template]

- 1. PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA's PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant's timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.<sup>12</sup>

Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., "Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*"). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a 'standard' PMR/PMC description may be employed [\[see Appendix B for examples\]](#).

- 2. PMR/PMC Milestones:** List the PMR/PMC milestones in the specified format.

Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered "core" PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.<sup>13</sup>

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<sup>12</sup> The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

<sup>13</sup> "Final" implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period

“Other” milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.<sup>14</sup>

## **SECTION C: PMR/PMC Rationale** [Click [here](#) to return to Section C of the template]

### **1. Describe the review issue and the goal of the study or clinical trial.**

This section should summarize the **rationale** for the study/trial. The section should **not** repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

*DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.*

*DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.*

### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.**

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

### **3. For FDAAA PMRs and 506B PMCs only**

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needed to create a well-designed study or clinical trial. See FDA guidance for industry, [Postmarketing Studies and Clinical Trials — Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act](#).

<sup>14</sup> Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B “reportable” PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

#### 4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS<sup>15</sup> and Sentinel’s ARIA<sup>16</sup> system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

##### **Question 4.a: identify the purpose of the study/clinical trial:**

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

##### **Questions 4.b-d: Explanation of whether FAERS and Sentinel’s postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.**

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency Memorandum*, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

##### **Question Q4.e: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.**

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

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<sup>15</sup> FDA Adverse Event Reporting System (FAERS)

<sup>16</sup> Active Risk Identification and Analysis (ARIA)

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

***Question Q4.f: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.***

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

**5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?**

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either “type of study” or “type of clinical trial.” Do not choose a option under both categories.

**SECTION D: PMR/PMC Additional information** [Click [here](#) to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

**1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?**

Select “yes” if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

**2. This study or clinical trial focuses on the following special population or circumstances:**

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select “not applicable.”

**3. (Complete if applicable) Additional comments about the PMR/PMC.**

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 “core” milestones).

Note: Additional milestones also must be tracked by the division (see [MAPP 6010.2](#), *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

**SECTION E: PMR/PMC Development Coordinator Statements** [Click [here](#) to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division’s Deputy Director for Safety) who will sign off on the completed Development Template.

**1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):**

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

**2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:**

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

**3. This PMR/PMC has been reviewed for clarity and consistency... reliability of drug quality.**

This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

## APPENDIX B

### Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

#### 1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Hepatic Impairment

Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.

- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)

Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#

Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

#### 2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy.

- Drug-Drug Interactions (gastric acid reducing agents)

Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.

- Drug-Drug Interactions-Induction

Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

- Anti-Drug Antibody Responses

Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient’s test sample at each sampling point.

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/s/  
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SUZANNE G DEMKO  
01/24/2018

JEFFERY L SUMMERS  
01/24/2018

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

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**Date of This Memorandum:** January 22, 2018  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 208700  
**Product Name and Strength:** Lutathera (lutetium Lu 177 dotatate) Injection,  
370 MBq/mL  
**Applicant/Sponsor Name:** Advanced Accelerator Applications USA Inc.  
**Submission Date:** January 3, 2018 and January 22, 2018  
**OSE RCM #:** 2017-1541-2  
**DMEPA Safety Evaluator:** Janine Stewart, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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#### 1 PURPOSE OF MEMO

DOP2 requested that we review the revised container label and carton labeling for Lutathera (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.<sup>a,b</sup>

#### 2 CONCLUSION

We acknowledge that the Applicant has expressed agreement that a perforated leadpot label would be advantageous, and will explore how best to implement the change in the future. We also acknowledge our prior recommendation to revise the statement “For intravenous infusion” to read “For Intravenous Infusion (b)(4)” is no longer applicable based on our

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<sup>a</sup> Stewart J. Label and Labeling Review for Lutathera (NDA 208700). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 09. RCM No.: 2017-1541.

<sup>b</sup> Stewart J. Label and Labeling Review Memorandum for Lutathera (NDA 208700). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Dec 26. RCM No.: 2017-1541-1.

understanding

(b) (4)

Thus, we have no further recommendations.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON JANUARY 22, 2018**

**Container label**



**Carton labeling**



**APPENDIX B. COVER LETTER RESPONSE TO DECEMBER 27, 2018 INFORMATION REQUEST  
SUBMITTED ON JANUARY 3, 2018**



3 January 2018

Patricia Keegan, M.D.  
Director, Division of Oncology Products 2  
CDER - Documents and Records Section  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Subject: NDA 208700 - LUTATHERA 370 MBq/mL (b)(4) (Lutetium Lu 177 Dotatate)  
Sequence 0062  
Response to Information Request IR-24 (Container Label and Carton Labeling)**

Attention: Nataliya Fesenko, PharmD, RPh, Regulatory Project Health Manager

Dear Dr. Keegan,

The response to Information Request [IR-24] received on December 27, 2017 is provided below. The response follows the restated FDA request.

**FDA Request:**

**General Comments (Container Label and Carton Labeling)**

1. Remove the (b)(4) statement, (b)(4) on the proposed container label (vial) and carton labeling (leadpot).
2. Revise the strength and dose statements to consistent units of measurement across all labels and labeling. We recommend using the units of measurement MBq followed by mCi in parenthesis. We remind you to revise the proposed Prescribing Information for consistency.
3. Revise the dosage form statement, ‘ (b)(4) ’, to read “Injection” (i.e., Lutathera (lutetium Lu 177 dotatate injection)).
4. Revise the statement “For intravenous infusion” to read “For Intravenous Infusion (b)(4)” in mixed case letters. We recommend this (b)(4)
5. Revise and relocate the statement “Single-Dose Vial” to appear underneath the (b)(4) statement and to read, “Single-Dose Vial. Discard Unused Portion”.

6. Add a "Usual Dose" statement on the side panel of the container label and carton Labeling to read "Usual dose: See Prescribing Information" in accordance with 21 CFR 201.55.
7. Ensure the radioactive warning symbol is accurate in shape and color, as is commonly seen in the US among drug products with radioactivity.

**Container Label (Vial)**

8. Revise the container label so activity at calibration time, lot number, and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed to optimize the clarity and the order of important product information on the Principal Display Panel (PDP). The example layout below [original FDA correspondence] demonstrates our recommendation only (Please note, the example need not be replicated with respect to size, spacing, color, etc.).

**Carton Labeling (Leadpot)**

9. Consider removing the statement "[redacted] (b)(4)". This statement clutters the label and does not appear necessary [redacted] (b)(4)
10. Consider providing perforated leadpot label with duplicate product information for use in the radiopharmacy. This would provide ease of use for verification and documentation by the radiopharmacy.

**Sponsor Response:**

The accompanying labels have been revised to incorporate all of the Agency's comments except Point 10. As a result, responding to each point, above, is not needed. However, there are two points which must be specifically addressed:

**Point 4.** While we have made this change as requested we do not feel this improves clarity. The wording "[redacted] (b)(4)" is misleading as we have noted previously. [redacted] (b)(4)

[redacted] We suggest replacing the statement "[redacted] (b)(4)" with "After proper connection to the infusion line".

**Point 10.** We agree that a perforated leadpot label would be advantageous. We will begin to look at how to best implement this change in the future.

Should you have questions or comments regarding this submission, please feel free to contact me by office phone (212.235.2381), mobile phone ([redacted] (b)(6)) or via email (victor.paulus@adacap.com).

Sincerely,



Victor G. Paulus, PhD  
Global Head, Regulatory Affairs

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/s/  
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JANINE A STEWART  
01/22/2018

CHI-MING TU  
01/22/2018

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

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**Date of This Memorandum:** December 26, 2017  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 208700  
**Product Name and Strength:** Lutathera (lutetium Lu 177 dotatate) Injection,  
370 MBq/mL  
**Applicant/Sponsor Name:** Advanced Accelerator Applications USA Inc.  
**Submission Date:** December 1, 2017  
**OSE RCM #:** 2017-1541-1  
**DMEPA Safety Evaluator:** Janine Stewart, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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## 1 PURPOSE OF MEMO

DOP2 requested that we review the revised container label and carton labeling for Lutathera (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

## 2 CONCLUSION

Because the Applicant did not address all of our recommendations in our previous review, the revised container label and carton labeling are unacceptable from a medication error perspective.

We note the order and prominence of product information on the proposed container label and carton labeling can be revised for improved readability and clarity. In addition, we note the product strength and dose designations use an inconsistent unit of measure (MBq vs. GBq) and do not consistently provide the equivalent mCi when comparing the container label and carton labeling to the Dosage and Administration section of the PI.

Additionally, the presentation of the established name is still inconsistent across proposed Prescribing Information (PI), container label, and carton labeling. We have contacted the Office of Product Quality (OPQ) for clarification and we defer to OPQ for the final determination of the established name. Further, we note the proposed Lutathera container label contains a strength expression which may confuse end users and potentiate the risk for wrong dose errors. In communication with OPQ on the fixed concentration statement, OPQ clarified that the Applicant should manufacture a product with radioactivity at time of calibration of 370 MBq/mL but then the radioactivity will degrade. Therefore, we provide recommendations in Section 3 to promote the safe use of this product.

## 3 RECOMMENDATIONS FOR ADVANCED ACCELERATOR APPLICATIONS USA INC.

We recommend the following be implemented prior to approval of this NDA:

### A. General Comments (Container label and carton labeling)

1. Remove the (b) (4) statement, (b) (4) (b) (4) on the proposed container label (vial) and carton labeling (leadpot).

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<sup>a</sup> Stewart J. Label and Labeling Review for Lutathera (NDA 208700). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 09. RCM No.: 2017-1541.

2. Revise the strength and dose statements to consistent units of measurement across all labels and labeling. We recommending using the units of measurement MBq followed by mCi in parenthesis. Reminder to revise the proposed Prescribing Information for consistency.
3. Revise the dosage form statement, “<sup>(b) (4)</sup>”, to read “Injection” (i.e. Lutathera (lutetium Lu 177 dotatate injection)).
4. Revise the statement “For intravenous infusion” to read “For Intravenous Infusion <sup>(b) (4)</sup>” in mixed case letters. We recommend this <sup>(b) (4)</sup>
5. Revise and relocate the statement “Single-Dose Vial” to appear underneath the “<sup>(b) (4)</sup>” statement and to read, “Single-Dose Vial. Discard Unused Portion”.
6. Add a “Usual Dose” statement on the side panel of the container label and carton labeling to read “Usual dose: <sup>(b) (4)</sup>” in accordance with 21 CFR 201.55
7. Ensure the radioactive warning symbol is accurate in shape and color as is commonly seen in the US among drug products with radioactivity.

B. Container Label (vial)

1. Revise the container label so activity at calibration time, lot number, and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed to optimize the clarity and the order of important product information on the Principal Display Panel (PDP). Example layout below demonstrates our recommendation only (not to size, spacing, color, etc.).



C. Carton Labeling (Leadpot)

1. Consider removing the statement “ (b) (4) ”. This statement clutters the label and does not appear necessary (b) (4)  
(b) (4)
2. Consider providing perforated leadpot label with duplicate product information for use in the radiopharmacy. This would provide ease of use for verification and documentation by the radiopharmacy.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON DECEMBER 1, 2017**

**Lutathera Vial Label**



**Lutathera Leadpot Label**



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/s/  
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JANINE A STEWART  
12/26/2017

CHI-MING TU  
12/26/2017



Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Memorandum**

**Date:** December 20, 2017                      **Date consulted:** September 25, 2017

**From:** Christos Mastroyannis, M.D., Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Tamara Johnson, M.D., MS, Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director  
Division of Pediatric and Maternal Health

**To:** Office of Hematology and Oncology Products/Division of Oncology  
Products 2 (OHOP/DOP2)

**Drug:** Lutathera (lutetium Lu 177)

**Drug Class:** Oncology Drugs, a somatostatin analogue

**NDA:** 208700

**Applicant:** Advanced Accelerator Applications USA, Inc. (AAA)

**Subject:** Pregnancy and Lactation Labeling as part of original NDA

**Proposed Indication:** Treatment of adult patients with [REDACTED] (b) (4)  
somatostatin receptor positive neuroendocrine tumors of midgut origin.

**Materials Reviewed:**

- DPMH consult request dated September 25, 2017 in DARRTS (Reference ID 4157679)
- Applicant's submission for NDA 208700 and Prescribing Information (PI) for Lutathera dated July 26, 2017.

**Consult Question:**

OHOP/DOP2 requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with PLLR format.

## INTRODUCTION

On July 26, 2017, Advanced Accelerator Applications USA, Inc. (AAA), the applicant, submitted a New Drug Application (NDA) 208700 for Lutathera (lutetium Lu 177). The proposed indication is the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors in adults. It is a 505(b)(1) NDA resubmission.

OHOP/DOP2 consulted the Division of Pediatric and Maternal Health (DPMH) on September 25, 2017, to provide input for appropriate labeling of the pregnancy and lactation subsections of Lutathera to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

## BACKGROUND

### Regulatory History

- The FDA has granted orphan drug designation (number of patients suffered of the disease are estimated to be <150,000) to Lutathera for the treatment of adult patients with (b) (4) neuroendocrine tumors (b) (4) on January 12, 2009)
- The NDA for Lutathera was initially submitted, in rolling fashion in accordance with Fast Track procedures, in April 2016.
- In the Complete Response (CR) letter sent by the FDA on December 19, 2016, the Agency informed the applicant that the application could not be approved due to missing data, uninterpretable data, data errors and unusable datasets.
- On July 26, 2017, AAA re-submitted NDA 208700 for Lutathera in response to the CR letter.

### Lutathera Drug Characteristics<sup>1</sup>

- Lutathera is a somatostatin receptor agonist with high affinity for somatostatin subtype 2 (sst2) receptors and coupled to the metal-ion chelating moiety, DOTA, and radiolabeled with <sup>177</sup>Lu. <sup>177</sup>Lu is a β-emitting radionuclide. The mean path length of the β-emission is about 2 mm, which is sufficient to effectively kill targeted tumour cells, and with only limited effect on neighboring non-target cells.
- The shelf-life of is 72 hours (b) (4) below 25 (b) (4) C.
- The molecular weight is 1609.6 Daltons
- The terminal half-life (*t*<sub>1/2</sub>) ranged from about 27.7 to 110 h (mean 71.2 h) About < 50% of the drug is bound to human plasma proteins at the expected plasma concentration in patients.

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<sup>1</sup> Applicant's submission, July 2017

- The drug is extensively eliminated by the kidney, mostly during the initial phase of the blood decay (about 60%) of the administered dose within the first 16/23 hours.
- Lutathera is supplied as a single dose vial, containing suitable amount of solution that allows delivery of 7.4 GBq of Lutathera at injection time.
- Because of Lutathera mechanism of action, there is some radioactivity retention in the kidneys; however concomitant administration of amino acids reduces renal uptake of radioactivity without altering tumor uptake.<sup>2</sup>
- The Physical Decay of Lutetium (Lu) 177 gives a half-life that is = 6.7 days; after 45 days , 0.010% of <sup>177</sup>Lu remains

## **REVIEW**

### ***Pregnancy***

As per applicant, AAA has not performed any clinical trials or nonclinical studies on the potential effects of Lutathera on pregnancy, and lactation. During the clinical trials, pregnancy and lactation were exclusion criterion. No pregnancies have been reported during the trials of the drug development program where the population of 121 women consisted of 8 subjects of reproductive potential and 113 menopausal or surgically sterilized. Lutathera should not be used during established or suspected pregnancy or when pregnancy has not been excluded, due to the risk associated with the ionizing radiation to the fetus and based on its mechanism of action. DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for Lutathera and use in pregnancy. No publications were identified.

### ***Lactation***

It is unknown whether lutetium Lu 177 is present in breast milk. A risk to the breastfed child associated with ionizing radiation cannot be excluded. Most common Grade 3-4 adverse reactions observed in adults with Lutathera include: lymphopenia, renal and hepatic toxicity, increased GGT, vomiting, nausea, elevated AST, and ALT, hyperglycemia and hypokalemia.

Also, in discussions with the Division, it was decided that the drug's accumulation in breast tissue is not of concern as it is with other radioactive drugs (like <sup>131</sup>iodine, which concentrates in breast tissue). The current thinking of the Division regarding the duration after treatment not to breastfeed is under discussion (women should not breastfeed during treatment and for 2 months after the final dose). DPMH also conducted a literature search in Toxnet/Lactmed databases in Hale TW Medications and Mother's Milk and Briggs GG and Freeman RK, Drugs in Pregnancy and Lactation for Lutathera and use in lactation. No publications were identified.

### ***Females and Males of Reproductive Potential***

Lutathera has the potential to cause fetal harm due to its mechanism of action and ionizing radiation; therefore, pregnancy status of females of reproductive potential prior to initiating treatment with Lutathera should be verified. Because the drug is genotoxic, females of reproductive potential should use effective contraception during treatment and for 7 months [as per recommendation by the OHOP

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<sup>2</sup> Kwekkeboom DJ, Krenning EP, Lebtahi R, Komminoth, Kos-Kudia B, de Herder WW, Plockinger U (2009). ENETS consensus guidelines for the standards of care in neuroendocrine tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs, *Neuroendocrinology* 2009; 90(2):220-226.

Pharmacology/Toxicology reviewer, based on half-life of the drug product and the decay time of <sup>177</sup>Lu (OHOP guidance for genotoxic drugs and radioactive decay/\_ *Cytotoxic Drugs (genotoxic, mutagenic) Females – 6 x terminal half-life (up to one year)*) following the final dose of Lutathera, while male patients with female partners of reproductive potential should use effective contraception during and for 4 months [as per OHOP guidance for genotoxic drugs and radioactive decay/ *Males – 3 months (one spermatogenesis cycle) for drugs with short half-life; 6 x terminal half-life + 3 months for drugs with longer half-lives*]-following the final dose of Lutathera. These contraception recommendations are based on OHOP’s contraception guidance.

During the drug development program, decreased inhibin-B and increased FSH was observed in men following Lutathera treatment, suggestive of transient infertility that recovered 12-18 months later. Men who wish to have a child may consider cryopreservation of sperm prior to initiating treatment with Lutathera.

## CONCLUSIONS

Lutathera labeling has been edited to comply with the PLLR. Lutathera, because of its mechanism of action and emission of ionizing radiation, may cause fetal harm. Pregnancy testing should always be performed prior to initiating treatment and effective contraception should be used during treatment and for 7 months after the last dose of Lutathera. It is unknown whether <sup>177</sup>lutetium Lu 177 is present in breast milk and its effects on the breastfed child or on milk production. A risk to the breastfed child associated with ionizing radiation cannot be excluded. Male patients with female partners of reproductive potential should use effective contraception during and for 4 months following the final dose of Lutathera. Because of the ionizing radiation effects on the testicles, and observed decrease in inhibin B and elevation of FSH, suggestive of male infertility, male patients interested in fathering a child, should consider sperm cryopreservation prior to treatment.

DPMH revised subsections 5.7, 5.8, 8.1, 8.2, and 8.3 and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

The Pregnancy and Lactation and Females and Males of Reproductive Potential subsections of Lutathera labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
  - The “Pregnancy” subsection of Lutathera labeling was formatted in the PLLR format to include the “Risk Summary” heading.
- **Lactation, Subsection 8.2**
  - The “Lactation” subsection of Lutathera labeling was formatted in the PLLR format to include the “Risk Summary” heading.
- **Females and Males of Reproductive Potential, Subsection 8.3**
  - Females and Males of Reproductive Potential subsection of Lutathera labeling was formatted to include the headings of “Pregnancy Testing”, “Contraception” for females and males and “Infertility” for males.

## RECOMMENDATIONS

DPMH has the following recommendations for Lutathera labeling.

### HIGHLIGHTS OF PRESCRIBING INFORMATION WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity: LUTATHERA can cause fetal harm. (b) (4)  
Advise females and males of reproductive potential to use effective contraception (5.7, 8.1, 8.3)
- Risk of Infertility: LUTATHERA may cause infertility. (0, 8.3)

### USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (0)

### FULL PRESCRIBING INFORMATION: CONTENTS

#### USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

### FULL PRESCRIBING INFORMATION

#### 5 WARNINGS AND PRECAUTIONS

##### 5.7 Embryo-Fetal Toxicity

Based on its mechanism of action, LUTATHERA can cause fetal harm [see *Clinical Pharmacology (12.1)*]. There are no available data on the use of LUTATHERA in pregnant women. No animal studies using lutetium Lu 177 dotatate have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm.

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose [see *Use in Specific Populations (8.1, 0)*].

##### 5.8 Risk of Infertility

LUTATHERA may cause infertility in males and females. The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy [see (b) (4) ] and *Use in Specific Populations (8.3)*].

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Risk Summary

Based on its mechanism of action, LUTATHERA can cause fetal harm [see *Clinical Pharmacology (12.1)*]. There are no available data on LUTATHERA use in pregnant women. No animal studies using lutetium Lu 177 Dotatate have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all

radiopharmaceuticals, including LUTATHERA, have the potential to cause fetal harm. Advise pregnant women of the risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

## **Lactation**

### Risk Summary

There are no data on the presence of lutetium Lu 177 Dotatate in human milk, or its effects on the breastfed infant or milk production. No lactation studies in animals have been conducted. Because of the potential risk for serious adverse reactions (b) (4)

(b) (4) in breastfed infants (b) (4), advise women not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose.

## **Females and Males of Reproductive Potential**

### Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating treatment with LUTATHERA [see *Use in Specific Populations* (b) (4)].

### Contraception

#### *Females*

(b) (4) LUTATHERA can cause fetal harm [see *Use in Specific Populations* (8.1)]. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the final dose of LUTATHERA.

#### *Males*

Based on its mechanism of action, advise male (b) (4) with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of LUTATHERA [see *Clinical Pharmacology* (12.1) and *Nonclinical Toxicology* (13.1)].

### Infertility

The recommended cumulative dose of 29.6 GBq of LUTATHERA results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

## **17 PATIENT COUNSELING INFORMATION**

### Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.7), *Use in Specific Populations* (8.1, 8.3)].

Advise females of reproductive potential to use effective contraception during treatment with LUTATHERA and for 7 months after the final dose [see *Use in Specific Populations* (8.1, 8.3)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with LUTATHERA and for 4 months after the final dose [see *Use in Specific Populations* (8.1, 8.3)].

Lactation

Advise females not to breastfeed during treatment with LUTATHERA and for 2.5 months after the final dose [see *Use in Specific Populations* (8.2)].

Infertility

Advise female and male patients that LUTATHERA may impair fertility [see *Warnings and Precautions* (5.8), *Use in Specific Populations* (8.3)].

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/s/  
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CHRISTOS MASTROYANNIS  
12/20/2017

LYNNE P YAO  
12/21/2017

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** December 4, 2017

**To:** Nataliya Fesenko, Pharm.D., R.Ph., Regulatory Project Manager  
Division of Oncology Products 2 (DOP 2)

Stacy Shord, Associate Director for Labeling, (DOP 2)

**From:** Carole Broadnax, Pharm.D., R.Ph., Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Susannah O'Donnell, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Lutathera (177 Lu-DOTA0-Tyr3-Octreotate)

**NDA:** 208700

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In response to DOP 2's consult request dated September 14, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for (Lutathera).

**PI and PPI/Medication Guide/IFU:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP 2 (Nataliya Fesenko) on November 20, 2017, and are provided below.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling received via a Sharepoint link sent by electronic mail from DOP 2 (Nataliya Fesenko) on November 21, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or [carole.broadnax@fda.hhs.gov](mailto:carole.broadnax@fda.hhs.gov).

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/s/  
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CAROLE C BROADNAX  
12/04/2017

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### **LABEL AND LABELING REVIEW**

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

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** November 09, 2017  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 208700  
**Product Name and Strength:** Lutathera (lutetium Lu 177 dotatate) Injection,  
370 MBq/mL  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Advanced Accelerator Applications USA Inc.  
**Submission Date:** April 28, 2016 and October 18, 2017  
**OSE RCM #:** 2017-1541  
**DMEPA Primary Reviewer:** Janine Stewart, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

---

## 1 REASON FOR REVIEW

As part of the NDA class 2 resubmission review for this new molecular entity Lutathera (lutetium Lu 177 dotatate) Injection, this review evaluates the proposed Lutathera container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that can lead to medication errors in response to a request from the Division of Oncology Products 2 (DOP2).

We note container labels and carton labeling were not submitted in this class 2 resubmission. Upon clarification with DOP2, DOP2 requested that we review the previous container labels and carton labeling submitted on April 28, 2016 from last review cycle.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G
Prescribing Information	H

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Lutathera Prescribing Information, the container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement.

We provide recommendations for improvement to the *Dosage and Administration, Dosage Forms and Strength*, and the *How Supplied* Sections of the proposed PI and have provided them in tracked changes in Appendix H.

We note the inconsistency of the established name which appears in the proposed Prescribing Information (PI) and on the proposed container label and carton labeling. We also note the

inconsistent use of package-type terms “single dose vial” and “(b) (4)” between the container label, carton labeling, and the PI. Therefore, we have contacted the Office of Product Quality (OPQ) for clarification and we defer to OPQ for the final determination of the established name and the package-type for this proposed product.

In addition, we note the proposed Lutathera container label contains a strength expression and a volume expression which may confuse end users and potentiate the risk for wrong dose errors. Further, the product strength designations use an inconsistent unit of measure when comparing the container labels and carton labeling to the Dosage and Administration section of the PI.

In addition, the order and prominence of product information on the proposed inner and outer carton labeling can be revised for improved readability and clarity. Moreover, the proposed inner and outer carton labeling can be improved by eliminating clutter and redundancy of information. Therefore, we provide recommendations in Section 4.2 in order to promote the safe use of this product.

#### **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the proposed Lutathera labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

##### **4.1 RECOMMENDATIONS FOR THE DIVISION**

###### **A. Prescribing Information**

1. Based on this review, we recommend revisions to the proposed PI in tracked changes for review and consideration by DOP2. See Appendix H for tracked change edits in the proposed PI.

##### **4.2 RECOMMENDATIONS FOR ADVANCED ACCELERATOR APPLICATIONS USA INC.**

We recommend the following be implemented prior to approval of this NDA:

###### **A. General Comments**

1. Revise the dosage form statement, “(b) (4)”, to read “Injection” (i.e. Lutathera (lutetium Lu 177 dotatate injection)).
2. Revise the statement (b) (4) to read “For Intravenous Infusion (b) (4)” in mixed case letters. We recommend this (b) (4)
3. Remove the “Rx Only” statement from the yellow “Caution: Radioactive Materials” warning symbol since the “Rx Only” statement already appears adjacent to the product information.

4. Provide justification or revise for consistent unit of measurement across all labeling to improve dosing instructions. We note inconsistent units of measurement when comparing the container labels and carton labeling (MBq, and mCi) to the Dosage and Administration section (GBq) of the PI. Inconsistent units of measurement for dosing increase the risk of wrong dose medication errors.
5. Consider adding the Unites States Distributor address to the container label and carton labeling to provide readily available US contact information for this product.
6. As proposed, the last two digits of the NDC numbers for the lead shielded carton labeling and the shipping carton labeling each have a different number. The lead shielded carton labeling and the shipping carton labeling each provide one vial of Lutathera. Therefore, having two different NDC numbers for the carton labeling could cause confusion when ordering the product and when verifying product selection prior to dispensing. Revise the NDC numbers so that the last two digits which indicate the commercial package size are the same between the lead shielded carton labeling and the shipping carton labeling (i.e. 69488-003-01).

#### B. Container Label

1. Remove the (b) (4) statement, “ (b) (4) ” from the container and carton labels. This (b) (4) statement (b) (4) may cause confusion and medication errors.
2. Remove the (b) (4) statement, “ (b) (4) ” from the container and carton labels. This (b) (4) statement (b) (4) may cause confusion and medication errors.
3. Revise the container label so activity, production time, lot and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed on the Principal Display Panel (PDP). This may be achieved by relocating other information to the side panel. Example layout below demonstrates our recommendation only (not to size, spacing, color, etc.). Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.



C. Carton Labeling

1. Revise and relocate the statement “(b) (4)” to appear underneath the “(b) (4)” statement and to read, “Single-Dose Vial. Discard Unused Portion”.
2. To make the label appear less crowded, (b) (4) provide only the name of the manufacturer and the city, state and country. The full manufacturer contact information appears in the Prescribing Information.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Lutathera that Advanced Accelerator Applications USA Inc. submitted on October 18, 2017.

<b>Table 2. Relevant Product Information for Lutathera</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	lutetium Lu 177 dotatate
<b>Indication</b>	For the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults.
<b>Route of Administration</b>	Intravenous
<b>Dosage Form</b>	(b) (4)
<b>Strength</b>	370 MBq/mL
<b>Dose and Frequency</b>	The recommended treatment regimen in adults consists in 4 administrations of 7.4 GBq (200 mCi) at the date and time of infusion. The recommended interval between each administration is 8 weeks (b) (4)
<b>How Supplied</b>	A (b) (4) single-dose vial
<b>Storage</b>	Room temperature storage (25 (b) (4) °C)
<b>Container Closure</b>	<p>The primary container of the drug product is a 30 mL sterile Type 1 glass vial. The vial is closed by a rubber stopper and crimp-sealed with an aluminum capsule with a hole.</p> <p>The drug product vial is placed within a cavity of the secondary container. The secondary packaging is a plastic sealed, lead shielded container.</p> <p>The secondary packaging is placed within a transport box for shipment to clinical settings. The secondary packaging and the transport box together comply with the requirements of Type A packaging. This packaging has no contact and no influence in term of quality for the product.</p>

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 8, 2017, we searched DMEPA's previous reviews using the term, Lutathera. Our search identified one previous review<sup>1</sup>. Given that our previous recommendations were not communicated to the Applicant during the review of the initial submission for this NDA and a Complete Response was issued for this NDA, our previous recommendations were not considered or implemented by the Applicant.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Lutathera labels and labeling submitted by Advanced Accelerator Applications USA Inc.

- Container label submitted on April 28, 2016
- Carton labeling submitted on April 28, 2016
- Prescribing Information submitted on October 18, 2017

### G.2 Label and Labeling Images

#### Container Label

(b) (4)



<sup>1</sup> Stewart, J. Label and Labeling Review for Lutathera (NDA 208700). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 22. RCM No.: 2016-993.

<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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JANINE A STEWART  
11/09/2017

CHI-MING TU  
11/13/2017

**Division of Medical Imaging  
Medical Officer Consultative Review  
October 6, 2017**

<b>NDA</b>	208700 resubmission SDN 36
<b>Sponsor</b>	AAA
<b>Product</b>	177Lu DOTATATE (Lutathera)
<b>Indication</b>	Adults for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults
<b>Requested by</b>	OHOP 9/26/17
<b>Due Date</b>	10/20/17
<b>Dose</b>	7.4 GBq (200 mCi) x 4 = 29.6 GBq (800 mCi) 8 <sup>(b)</sup> <sub>(4)</sub> -week intervals
<b>Reviewer</b>	Cindy Welsh
<b>Deputy Director</b>	Alex Gorovets
<b>OHOP request</b>	Evaluation of radiation dosimetry (NETTER 1 dosimetry sub-study report) and expected organ and bone marrow exposure from treatment with this radionuclide therapy.

**Dosimetry**

The sponsor submitted an amended version of the NETTER 1 dosimetry sub-study report. The changes included updating the length of follow up (cutoff date June 30, 2016), adverse events, and minor changes to the dosimetry tables. The new information does not warrant change to my consult response from 2016.

**With respect to labeling section 2.6**

The sponsor appears to have calculated doses based upon the data of the 20 patients in the dosimetry substudy (see table 16.3.2). The numbers were summed and then the mean was calculated and recorded in the chart along with the standard deviation for 1 cycle and then for the cumulative 4 cycles. The dosimetry of Xofigo was based upon N=5.

Examples of the header rows of the dosimetry section of various therapeutic radiopharmaceutical labels are shown below. DMIP has no recommended standardization for dosimetry tables other than the need to use SI units (Gy/Bq and not rad/mCi) and defers to OHOP with respect to format.

ORGAN	Absorbed dose per unit activity (Gy/GBq) (N=20)		Calculated absorbed dose for 4 x 7.4 GBq (29.6 GBq cumulative administered activity) (Gy)	
	Mean	SD	Mean	SD

The format of this table differs from that of Xofigo (administered in cycles) and Zevalin (single administration).

Xofigo

Target Organ	Mean (Gy/MBq)	Mean (rad/mCi)	Coefficient of Variation (%)
--------------	---------------	----------------	------------------------------

Zevalin

Organ	Y90 Zevalin cGy/mCi (mGy/MBq)	
	median	range

Furthermore, the sponsor proposes the following in section 2.6 of the label:



DMIP defers to the ADL in your division but notes that as written this information may be considered promotional and/or incorrect (see yellow highlights), is not consistent with other therapeutic labels, and that this information may be more appropriate when moved/edited to other sections of the label. As an example, the NETTER-1 dosimetry substudy (page 71) notes:

“Notwithstanding the low degree of observed toxicity, possible correlations with radiation doses were investigated. No clear correlation was evident, except for platelet acute toxicity, Hb and Lym late toxicity (the mean absorbed doses to red marrow were 0.6, 0.7, 0.8 Gy for G0 in patients without PLT, Hb and Lym toxicity and 1.2, 1.1, 1.3 Gy in patients  $G \geq 1$  PLT, Hb and Lym toxicities and 1.2 for G1, respectively).”

The dosimetry section of the label usually states the method that the sponsor used to calculate the doses. (DMIP notes that FDA labeling has evolved these labels were written in 2013).

As an example, the Xofigo label:

Dosimetry

The absorbed radiation doses in major organs were calculated based on clinical biodistribution data in five patients with castration-resistant prostate cancer. Calculations of absorbed radiation doses were performed using OLINDA/EXM (Organ Level Internal Dose Assessment/EXponential Modeling), a software program based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For radium-223, which is primarily an alpha particle-emitter, assumptions were made for intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed radiation dose calculations for Xofigo, considering its observed biodistribution and specific characteristics. The calculated absorbed radiation doses to different organs are listed in Table 2. The organs with highest absorbed radiation doses were bone (osteogenic cells), red marrow, upper large intestine wall, and lower large intestine wall. The calculated absorbed doses to other organs are lower.

And an example from the Zevalin label:

2.5 Radiation Dosimetry (b) (4), estimations of radiation-absorbed doses for Y-90 Zevalin were performed using sequential whole body images and the MIRDOSE 3 software program. The estimated radiation absorbed doses to organs and marrow from a course of the Zevalin therapeutic regimen are summarized in (b) (4). Absorbed dose estimates for the lower large intestine, upper large intestine, and small intestine have been modified from the standard MIRDOSE 3 output to account for the assumption that activity is within the intestine wall rather than the intestine contents.

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/s/  
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CYNTHIA A WELSH  
10/06/2017

ALEXANDER GOROVETS  
10/06/2017

## Office of Hematology and Oncology Products Memorandum

<b>NDA</b>	208700
<b>Applicant</b>	Advanced Accelerator Applications USA, Inc. (AAA)
<b>Link to EDR</b>	<a href="#">\CDSESUB1/evsprod/NDA208700</a>
<b>Submission Date(s)</b>	March 31, 2016; April 18, 2016; April 28, 2016; October 18, 2016; October 19, 2016
<b>Submission Type</b>	New Molecular Entity
<b>Priority or Standard</b>	Priority
<b>Proposed Trade Name</b>	LUTATHERA
<b>Established Name</b>	<sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate
<b>Dosage Form and Strength</b>	7.4 GBq every 8 weeks for four doses
<b>Route of Administration</b>	Intravenous
<b>Proposed Indication</b>	Treatment of adult patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors
<b>Regulatory Project Manager</b>	Susan Truitt

The Division Director's review is complete and has been added to the NDA/BLA Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Approval of this application is not recommended in its present form, and a Complete Response Letter listing the deficiencies identified in this NDA will be issued to the applicant. Please refer to the Multi-disciplinary Review and Evaluation for additional details.

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STEVEN J LEMERY  
12/06/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** November 21, 2016

**To:** Susan Truitt, R.N., M.S.  
Regulatory Health Project Manager  
Division of Oncology Drug Products 2 (DOP 2)

**From:** Carole Broadnax, R.Ph., Pharm.D.  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **NDA 208700**  
LUTATHERA (<sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate)

---

OPDP acknowledges receipt of the May 2, 2016, consult request from DOP 2 for the proposed product labeling (PI and carton/container) for LUTATHERA (177Lu-DOTA0-Tyr3-Octreotate). OPDP notes DOP 2 indicated a Complete Response letter will be issued for this application. As such, final labeling negotiations will not be initiated during the current review cycle. Therefore, OPDP will not provide comments on the proposed product labeling during this review cycle.

OPDP requests that DOP 2 submit a new consult request during a subsequent review cycle in order for OPDP to provide comments regarding labeling for this application.

If you have any questions, please feel free to contact me by phone at 301-796-0575 or by email at [Carole.Broadnax@fda.hhs.gov](mailto:Carole.Broadnax@fda.hhs.gov).

Thank you!

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/s/  
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CAROLE C BROADNAX  
11/21/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**TO:** NDA 208700

**FROM:** Denise Johnson-Lyles, Ph.D., Senior Regulatory Project Manager  
Division of Pediatric and Maternal Health (DPMH)

**SUBJECT:** Division of Oncology Products 2 (DOP2) consult request to DPMH requesting maternal health labeling review, DARRTS Reference ID: 3933494

**DRUG:** Lutathera

DOP2 submitted a consult request to DPMH dated May 18, 2016, asking for maternal health (pregnancy and lactation) labeling review for the above referenced, NDA 208700.

DPMH participated in internal team meetings for this application, including a team meeting held on October 28, 2016. During the October 28<sup>th</sup> meeting, the team was notified of the plan to issue a Complete Response (CR) letter to the NDA applicant. The plan for a CR action was also confirmed in an email to the review team on the same October date.

The decision to issue a CR letter to the NDA applicant was made prior to DPMH completing and presenting maternal health labeling recommendations for this NDA. If labeling review resumes upon resubmission of the NDA, DPMH may be re-consulted for maternal health labeling review. DPMH has no further comment at this time. This memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer– Christos Mastroyannis  
DPMH Maternal Health Team Leader – Tamara Johnson  
DPMH Division Director - Lynne Yao  
DPMH RPM – Denise Johnson-Lyles

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/s/

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DENISE N JOHNSON-LYLES  
11/08/2016  
DPMH RPM Closeout

## Clinical Inspection Summary

<b>Date</b>	October 7, 2016
<b>From</b>	Lauren Iacono-Connors, Reviewer
<b>To</b>	Susan Truitt, Regulatory Project Manager Joohee Sul, Clinical Reviewer Division of Oncology Products 2
<b>NDA #</b>	208700
<b>Applicant</b>	Advanced Accelerator Applications USA, Inc.
<b>Drug</b>	Lutathera ( <sup>177</sup> Lu-DOTA0-Tyr <sup>3</sup> -Octreotate; established name requested is lutetium Lu <sup>177</sup> dotatate)
<b>NME</b>	Yes
<b>Therapeutic Classification</b>	Priority
<b>Proposed Indication</b>	Treatment of adult patients with (b) (4) somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEPNETs), including foregut, midgut, and hindgut [neuroendocrine tumors (b) (4)]
<b>Consultation Request Date</b>	May 26, 2016
<b>Summary Goal Date</b>	September 28, 2016 (To be extended based on pending IR)
<b>Action Goal Date</b>	December 28, 2016
<b>PDUFA Date</b>	December 28, 2016

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from NETTER-1 (AAA-III-01) were submitted to the Agency in support of NDA 208700. Four clinical sites, Dr. Matthew Kulke (Site US08), Dr. James C. Yao (Site US12), Dr. Jonathan R. Strosberg, (Site US13), Dr. Andrew E. Hendifar (Site US14), and two CROs (b) (4), of Study AAA-III-01, were selected for audit.

The primary efficacy endpoint, Progress Free Survival (PFS), as reported in the Clinical Study Report (CSR) was verified with the source records generated at the inspected clinical sites and at the CRO for a sample of clinical sites. There were no significant deficiencies. The inspections of Dr. Matthew Kulke (Site US08), Dr. James C. Yao (Site US12), (b) (4) found no significant deficiencies associated with Study AAA-III-01 conduct.

European Medicines Agency (EMA) inspections (independent of FDA inspections) of Dr. Jonathan R. Strosberg, (Site US13) and Dr. Andrew E. Hendifar (Site US14) found discrepancies between source records and data listings submitted to the application but based on preliminary information, these discrepancies do not appear to impact overall safety or efficacy outcomes.

The data used in the CSR from Study AAA-III-01, submitted to the Agency in support of NDA 208700 accurately reflects what was in the clinical database at the data cutoff date.

## II. BACKGROUND

Advanced Accelerator Applications SA (AAA) seeks approval of lutathera ( $^{177}\text{Lu}$ -DOTA0-Tyr<sup>3</sup>-Octreotate) for the treatment of patients with [REDACTED] neuroendocrine tumors [REDACTED].

[REDACTED]. FDA granted Orphan Drug Designation for Lutathera. This request is based on the results from Study NETTER-1 (AAA-III-01) a multicenter, stratified, open, randomized, comparator-controlled, parallel group phase III study comparing treatment with  $^{177}\text{Lu}$ -DOTA0-Tyr<sup>3</sup>-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors. The study enrolled and screened 341 subjects and 229 subjects were randomized 1:1 (116 Lutathera, 113 Octreotide LAR) at 41 clinical centers in 7 countries. There were 14 clinical centers in the United States.

Study Period: Study initiation date (first subject randomized): September 6, 2012

Study completion date (primary end-point database lock): September 14, 2015

Primary efficacy endpoint:

To compare Progression Free Survival (PFS) after treatment with Lutathera plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, progressive (as determined by RECIST Criteria), somatostatin receptor positive, well-differentiated neuroendocrine tumors of the small bowel.

Sponsor's interpretation of primary efficacy outcome: Time to event. PFS was defined as the time from randomization to documented, centrally assessed disease progression, as evaluated by the Independent Reading Center (IRC), and death due to any cause.

Objectives of Inspections:

- a. Verify primary efficacy endpoint of PFS determined by the investigator and the IRC.
- b. Verify key secondary efficacy endpoints for a sample of enrolled subjects:
  - Objective Response, defined as confirmation of a PR or CR event.
  - Overall survival (OS)
- c. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- d. General compliance with the investigational plan.

**III. RESULTS (by site):**

<b>Name of CI, Site #, Address</b>	<b>Protocol # and # of Subjects</b>	<b>Inspection Date</b>	<b>Final Classification</b>
<b>CI#1: Matthew Kulke, M.D. Site #US08</b> Dana-Farber/Brigham and Women's Cancer Center 450 Brookline Avenue Boston, MA 02215	Protocols: NETTER-1 (AAA-III-01)  Number of Subjects Enrolled: 11	June 14-21, 2016	NAI
<b>CI#2: James C. Yao, M.D. Site #US12</b> The University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd, Houston, TX 77030	Protocols: NETTER-1 (AAA-III-01)  Number of Subjects Enrolled: 15	July 7-13, 2016	NAI
<b>CRO 1: Location of TMF</b>  (b) (4)	Protocols: NETTER-1 (AAA-III-01)  Site Numbers: US13, US14, US12, US08, US01, and US11	September 5- 9, 2016	Pending  Interim classification: NAI
<b>CRO 2: Performed as the Independent Reading Center (IRC) for Image Assessment</b>  (b) (4)	Protocols: NETTER-1 (AAA-III-01)  Site Numbers: US13, US14, US12, US08, US01, and US11	August 29- September 2, 2016	Pending  Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**1. Dr. Matthew Kulke, M.D. (Site US08)**

The inspection reviewed the conduct of one clinical study (AAA-III-01). The site screened 15 subjects and 11 were enrolled and treated. A complete record review was done for all 15 screened subjects. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 208700, focusing on

inclusion/exclusion criteria compliance, adverse events, randomization, and efficacy endpoint verification. Assessment of study oversight and conduct by Dr. Kulke included AE reporting practices and general protocol compliance.

The inspection revealed no significant deficiencies. The efficacy endpoint data found at the site corroborated the primary efficacy outcome measure of PFS as determined by a central IRC. PFS as determined by the clinical investigator and OS was verified. There was no evidence of under-reporting of AEs.

The data from Site US08, associated with Study AAA-III-01 appear reliable based on available information.

## **2. Dr. James C. Yao, M.D. (Site US12)**

The inspection reviewed the conduct of one clinical study (AAA-III-01). The site screened 21 subjects and 15 were enrolled and treated. At the time of this inspection 10 subjects had completed the study and are in long term follow up. The remaining five subjects discontinued due to progressive disease. A complete record review was done for seven screened subjects.

The inspection revealed no significant deficiencies. The efficacy endpoint data found at the site corroborated the primary efficacy outcome measure of PFS as determined by a central IRC. PFS as determined by the clinical investigator and OS was verified. There was no evidence of under-reporting of AEs.

The data from Site US12, associated with Study AAA-III-01, appear reliable based on available information.

## **3. CRO 1: [REDACTED] (b) (4)**

This CRO inspection assignment was issued to review the conduct of one clinical study (AAA-III-01), performed in support of NDA 208700. The inspection focused on the CRO's control, oversight, and management of Study AAA-III-01.

[REDACTED] (b) (4) was responsible for continuous on-site monitoring of the study to ensure that patients' human rights, safety, and well-being were protected, that the study was conducted in adherence to the current protocol, ICH, and GCP and all applicable local, national and international regulations, and that the data reported by the investigator or designee were accurate, complete, and verifiable with the source documents. The CRO was also responsible for national and international clinical project management, data management, medical review, medical coding, statistical analysis and report writing, under the direction of the Sponsor (AAA). In addition, all the statistical analyses were performed by [REDACTED] (b) (4) in accordance with the SAP which was finalized before database lock. Monitoring records were reviewed from six clinical sites. The CRO contract agreement required 15 periodic monitoring visits, in addition to the trial selection visit, site initiation visit, and close-out visit at each site. Actions taken by the CRO to bring non-compliant clinical sites into compliance were also assessed. All

contract agreements and the sponsor responsibility transfer agreement were reviewed. Reporting practices for adverse events and serious adverse events were also reviewed. Clinical site files were reviewed for Form FDA 1572s, clinical investigator CVs, and completed financial disclosure documentation.

(b) (4) maintained adequate oversight over the study. There was no evidence of under-reporting of adverse events/serious adverse events. The primary efficacy endpoint was PFS, defined as the time from randomization to documented, centrally assessed disease progression determined by the IRC, CRO (b) (4). Compliance with the investigational plan appeared to be adequate. Monitoring appeared adequate. Review of investigator agreements and financial disclosure documentation found no deficiencies.

The data from this CRO, associated with Study AAA-III-01, in the CSR submitted to the Agency in support of NDA 208700, appear reliable.

#### 4. CRO 2: (b) (4)

This inspection was issued to review the conduct of one clinical study (AAA-III-01), performed in support of NDA 208700. The inspection focused primarily on assessing the accuracy of the tumor response and disease progression source records (images and interpretation) as it pertains to the Agreement between (b) (4) (on behalf of study sponsor AAA) for Study AAA-III-01 per (b) (4) Core Image Manual V1.6. Subject source documents/records generated by (b) (4) for six clinical sites, 101 randomized subjects (44 % of all randomized subjects) were compared to the eCRF and data listings submitted to NDA 208700. Assessment of (b) (4) conduct of the IRC responsibilities included training, education, and qualifications of radiologists, correspondence with clinical sites/sponsor, quality assurance, data collection and management, and Core Image Manual V1.6 review and adherence.

All reviewed subjects' PFS as determined by the CRO radiologists were verified against the data listings submitted to the application. There were no discrepancies. There was no evidence of CRO non-compliance with the investigational plan.

The data from this CRO, associated with Study AAA-III-01, in the CSR submitted to the Agency in support of NDA 208700, appear reliable.

**The clinical investigators Dr. Jonathan R. Strosberg (Site US13) and Dr. Andrew E. Hendifar (Site US14) preliminary inspectional findings are described below. These clinical site inspections were conducted by the EMA.**

#### 5. Dr. Jonathan R. Strosberg (Site US13) and Dr. Andrew E. Hendifar (Site US14)

These inspections were performed by EMA inspectors as a routine data audit for their submission of a similar application for the use of lutathera for the treatment of

GEPNETs. The key study supporting the application submitted to EMA was Study AAA-III-01. The inspection reviewed the conduct of Study AAA-III-01. A standard data audit by EMA inspectors considers overall study conduct, organization structure, and study oversight and control. Study personnel qualifications and training, sponsor and IRB correspondence, data management, clinical monitoring, safety reporting and source data verification are also considered during an EMA inspection. Study source documents/records of enrolled subjects were compared to the eCRF and similar data listings as those included in the CSR submitted to NDA 208700.

(b) (4)

*OSI Reviewers Note: On October 5, 2016, OSI reviewer, Lauren Iacono-Connors communicated the FDA and EMA inspectional findings for this application to Suzanne Demko, CDTL for the application review team.*

(b) (4)

*Suzanne Demko also informed that the*

*review team has had a number of problems working with the datasets submitted to the application and they have been unable to reproduce the sponsor's analyses included in the CSR. For these reasons DOP2 requested that the sponsor submit updated datasets for Study AAA-III-01. The updated datasets are expected by October 11, 2016. The actions taken by DOP2 should mitigate database integrity concerns raised by the EMA inspectors. Since this is an ongoing study, this management of the database may or may not be valid.*

{See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page }

Susan Thompson, M.D.  
Team Leader  
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Kassa Ayalew, M.D., M.P.H  
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Office of Scientific Investigations

CC:

Central Doc. Rm. NDA #208700

DOP2/Division Director/Patricia Keegan

DOP2/Clinical Team Leader/Suzanne Demko

DOP2/Project Manager/Susan Truitt

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OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/Team Leader/Susan D. Thompson

OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors

OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague

OSI/Database PM/Dana Walters

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LAUREN C IACONO-CONNORS  
10/07/2016

SUSAN D THOMPSON  
10/07/2016

KASSA AYALEW  
10/12/2016

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## **LABEL AND LABELING REVIEW**

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

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	August 22, 2016
<b>Requesting Office or Division:</b>	Division of Oncology Products 2 (DOP2)
<b>Application Type and Number:</b>	NDA 208700
<b>Product Name and Strength:</b>	Lutathera (lutetium Lu 177 dotatate) Injection, 370 MBq/mL
<b>Product Type:</b>	Single Ingredient Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Advanced Accelerator Applications USA Inc.
<b>Submission Date:</b>	April 28, 2016 and June 13, 2016
<b>OSE RCM #:</b>	2016-993
<b>DMEPA Primary Reviewer:</b>	Janine Stewart, PharmD
<b>DMEPA Team Leader:</b>	Chi-Ming (Alice) Tu, PharmD

---

## 1 REASON FOR REVIEW

As part of the NDA review for this new molecular entity Lutathera (lutetium Lu 177 dotatate) Injection, this review evaluates the proposed Lutathera container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that can lead to medication errors in response to a request from the Division of Oncology Products 2 (DOP2).

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B- N/A
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G
Prescribing Information	H

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Lutathera Prescribing Information, the container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement.

We provide recommendations for improvement to the *Dosage and Administration*, *Dosage Forms and Strength*, and the *How Supplied* Sections of the proposed PI and have provided them in tracked changes in Appendix H.

We note the inconsistency of the established name which appears in the proposed Prescribing Information (PI) and on the proposed container label and carton labeling. We also note the inconsistent use of package-type terms “single dose vial” and “(b) (4)” between the container label, carton labeling, and the PI. Therefore, we have contacted the Office of Product Quality (OPQ) for clarification and we defer to OPQ for the final determination of the established name and the package-type for this proposed product.

In addition, we note the proposed Lutathera container label contains a strength expression and a volume expression which may confuse end users and potentiate the risk for wrong dose errors. Further, the product strength designations use an inconsistent unit of measure when comparing the container labels and carton labeling to the Dosage and Administration section of the PI.

In addition, the order and prominence of product information on the proposed inner and outer carton labeling can be revised for improved readability and clarity. Moreover, the proposed inner and outer carton labeling can be improved by eliminating clutter and redundancy of information. Therefore, we provide recommendations in Section 4.2 in order to promote the safe use of this product.

#### **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the proposed Lutathera labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

##### **4.1 RECOMMENDATIONS FOR THE DIVISION**

###### **A. Prescribing Information**

1. Based on this review, we recommend revisions to the proposed PI in tracked changes for review and consideration by DOP2. See Appendix H for tracked change edits in the proposed PI.

##### **4.2 RECOMMENDATIONS FOR ADVANCED ACCELERATOR APPLICATIONS USA INC.**

We recommend the following be implemented prior to approval of this NDA:

###### **A. General Comments**

1. Revise the dosage form statement, [REDACTED] <sup>(b) (4)</sup>, to read "Injection" (i.e. Lutathera (lutetium Lu 177 dotatate injection)).
2. Remove the "Rx Only" statement from the yellow "Caution: Radioactive Materials" warning symbol since the "Rx Only" statement already appears adjacent to the product information.
3. Provide justification or revise for consistent unit of measurement across all labeling to improve dosing instructions. We note inconsistent units of measurement when comparing the container labels and carton labeling (MBq, and mCi) to the Dosage and Administration section (GBq) of the PI. Inconsistent units of measurement for dosing increase the risk of wrong dose medication errors.

4. Consider adding the United States Distributor address to the container label and carton labeling to provide readily available US contact information for this product.
5. As proposed, the last two digits of the NDC numbers for the lead shielded carton labeling and the shipping carton labeling each have a different number. The lead shielded carton labeling and the shipping carton labeling each provide one vial of Lutathera. Therefore, having two different NDC numbers for the carton labeling could cause confusion when ordering the product and when verifying product selection prior to dispensing. Revise the NDC numbers so that the last two digits which indicate the commercial package size are the same between the lead shielded carton labeling and the shipping carton labeling (i.e. 69488-003-01).

B. Container Label

1. Remove the (b) (4) statement, (b) (4) from the container and carton labels. This (b) (4) statement (b) (4) may cause confusion and medication errors.
2. Remove the (b) (4) statement, (b) (4) from the container and carton labels. This (b) (4) statement (b) (4) and may cause confusion and medication errors.
3. Revise the container label so activity, production time, lot and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed on the Principal Display Panel (PDP). This may be achieved by relocating other information to the side panel. Example layout below demonstrates our recommendation only (not to size, spacing, color, etc.). Of note, we recommend mix case letters (b) (4) instead of all upper case to improve readability. Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.



C. Carton Labeling

1. Revise and relocate the statement “ (b) (4) ” to appear underneath the (b) (4) ” statement and to read, “Single-Dose Vial. Discard Unused Portion”.
2. To make the label appear less crowded, (b) (4) provide only the name of the manufacturer and the city, state and country. The full manufacturer contact information appears in the Prescribing Information.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Lutathera that Advanced Accelerator Applications USA Inc. submitted on June 13, 2016.

<b>Table 2. Relevant Product Information for Lutathera</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	lutetium Lu 177 dotatate
<b>Indication</b>	For the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults.
<b>Route of Administration</b>	Intravenous
<b>Dosage Form</b>	(b) (4)
<b>Strength</b>	370 MBq/mL
<b>Dose and Frequency</b>	The recommended treatment regimen in adults consists in 4 administrations of 7.4 GBq (200 mCi) at the date and time of infusion. The recommended interval between each administration is 8 weeks which could be extended up to 16 weeks in case of dose modifying toxicity
<b>How Supplied</b>	A (b) (4) single-dose vial
<b>Storage</b>	Room temperature storage (25 (b) (4) °C)
<b>Container Closure</b>	<p>The primary container of the drug product is a 30 mL sterile Type 1 glass vial. The vial is closed by a rubber stopper and crimp-sealed with an aluminum capsule with a hole.</p> <p>The drug product vial is placed within a cavity of the secondary container. The secondary packaging is a plastic sealed, lead shielded container.</p> <p>The secondary packaging is placed within a transport box for shipment to clinical settings. The secondary packaging and the transport box together comply with the requirements of Type A packaging. This packaging has no contact and no influence in term of quality for the product.</p>

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Lutathera labels and labeling submitted by Advanced Accelerator Applications USA Inc.

- Container label submitted on April 28, 2016
- Carton labeling submitted on April 28, 2016
- Prescribing Information submitted on June 13, 2016

### **G.2 Label and Labeling Images**

#### **Container Label**



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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

**Inner Leadpot Carton Labeling**

(b) (4)



**Outer Shipping Carton Labeling**

(b) (4)



**APPENDIX H. PRESCRIBING INFORMATION**

APPEARS THIS WAY ON ORIGINAL

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANINE A STEWART  
08/22/2016

CHI-MING TU  
08/22/2016

**Division of Medical Imaging  
Medical Officer Consultative Review  
August 18, 2016**

<b>NDA</b>	208700
<b>Sponsor</b>	AAA
<b>Product</b>	177Lu DOTATATE (Lutathera)
<b>Indication</b>	Adults for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults
<b>Requested by</b>	OHOP
<b>Dose</b>	7.4 GBq (200 mCi) x 4 = 29.6 GBq (800 mCi) 8 <sup>(b)</sup> <sub>(4)</sub> -week intervals
<b>Reviewer</b>	Cindy Welsh
<b>Deputy Director</b>	Alex Gorovets

From the OHOP consult request:

1. Please evaluate the criteria for the OctreoScan scintigraphy results to determine eligibility for the studies included in the NDA.
2. Please provide a general review of the dosimetry plan, study drug administration parameters, dose and dosing regimen for Lutathera.
3. Please also comment on the acceptability of the amino acid solutions used in the studies (Vamin 18 in the EU and Aminosyn II 10% in the US).
4. Please provide any additional comments/concerns you may have with the data submitted in the application.

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**1. Please evaluate the criteria for the OctreoScan scintigraphy results to determine eligibility for the studies included in the NDA.**

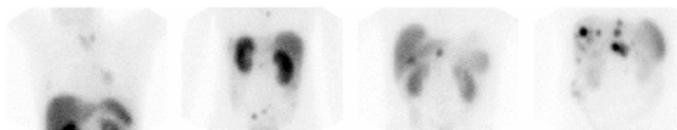
DMIP response:

The OctreoScan scintigraphy criteria for the 2 protocols are excerpted from the protocols and are shown below.

**Erasmus protocol criteria:**

From Appendix 4 OctreoScan Uptake and Extent Scale (source: sponsor NDA submission section 5.3.5.1 Erasmus protocol page 29)

The intensity of tumor uptake and the extent of tumor burden is to be scored according to simple scaling systems:



Tumor Uptake: 1) < Liver (Excluded) 2) ≈ Liver 3) > Liver 4) Very intense (>>Kidneys, spleen)  
Grade OctreoScan®:



Tumor mass on OctreoScan®: Limited Moderate Extensive

**Limited:** Up to 5 sites in one part of the body (head/neck, chest, upper abdomen, lower abdomen).

**Moderate:** Multiple sites in up to 2 sites of the body. Neither qualifying for limited nor for extensive.

**Extensive:** Many tumor sites in  $\geq 2$  parts of the body. Usually a combination of extensive liver and lymph node involvement or diffuse skeletal metastases. Diffuse liver metastases with limited abdominal involvement does not qualify.

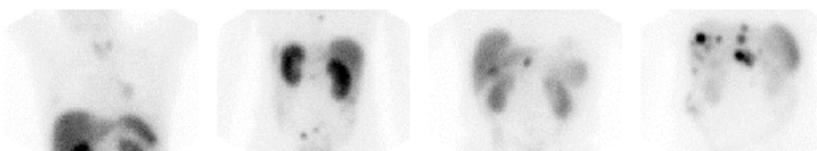
**NETTER protocol criteria** (source: sponsor NDA submission section 5.3.5.1 NETTER protocol pages 123-136)

From Appendix 5 – OctreoScan® Tumor Uptake and Extent of Tumor Burden Scales  
The Tumor Uptake and the Extent of Tumor Burden scores are based solely on the planar images obtained at 24 hours after administration of OctreoScan® according to the Tumor Scoring methods described below. Planar image acquisition is to be performed according to the technical protocol specified in Appendix 6 - Part 1.

#### Tumor Scoring

The intensity of Tumor Uptake and the Extent of Tumor Burden is to be scored according to simple scaling systems.

The Tumor Uptake score is determined by comparing the uptake of OctreoScan® (24 hour planar scintigrams) in the selected tumor to the uptake observed in the liver according to the following examples:



Tumour Uptake:  
Grade OctreoScan®:      1) < Liver (Excluded)      2) ≈ Liver      3) > Liver      4) Very intense (>>Kidneys, spleen)

The Extent of Tumour Burden score is determined by assessing the number of OctreoScan® positive tumours and is scored according to following examples and descriptions:



Tumour Burden score OctreoScan®:      Limited      Moderate      Extensive

Limited: Up to 5 sites in one part of the body (head/neck, chest, upper abdomen, lower abdomen).

Moderate: Multiple metastatic lesions in up to 2 parts of the body, neither qualifying for limited nor for extensive.

Extensive: Many tumor sites in ≥ 2 parts of the body, usually a combination of extensive liver and lymph node involvement or diffuse skeletal metastases; diffuse liver metastases with limited abdominal involvement does not qualify.

From Appendix 6

OctreoScan® Planar Imaging Protocol (ENETS Guidelines)

ENETS Guidelines

Kwekkeboom et al, 2009. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Somatostatin Receptor Imaging with 111In-Pentetreotide

*Neuroendocrinology* 90:184–189. DOI: 10.1159/000225946.

OctreoScan® Summary of Product Characteristics

**Reviewer comment:**

- ***The definitions used in the protocols are consistent with professional guidelines. Note that contributors to the professional guidelines participated in the studies submitted in the application.***
- ***At the time that this therapeutic product (Lutathera) was being developed, the only approved imaging agent for this disease was OctreoScan SPECT. The active moiety in the imaging agent binds to the same receptor (SSTR2) as the therapeutic product (Lutathera) and has been used in clinical practice (off label) to determine patient eligibility for the therapeutic product.***
- ***Over the past ~decade, with the development of CMC advances, other imaging agents (e.g. 68Ga DOTA –TATE, -TOC, and -NOC) were being developed for the same patient population (patients with SSTR2 tumors) that can be made on site (i.e. does not require a cyclotron), and have better image resolution, shorter imaging***

*parameters, and decreased radiation dose to the patient. Ga68 DOTATATE was approved in June 2016 (same sponsor – AAA) with a localization indication. The product does not have an indication for patient management or determination of eligibility for treatment with the therapeutic product although it is likely that the product will be used in that fashion as practice of medicine as that has been occurring in the clinical setting in the US and EU already.*

(b) (4)

(b) (4)

- *Given the recent approval of the 68Ga Dotatate PET product for this patient population, it is likely that OctreoScan will not be used regularly in the clinic for this patient population for the determination of PRRT eligibility.*
- *The definitions of limited, moderate and extensive tumor burden are consistent across the protocols. While these protocols categorized the tumor scoring and uptake, it is likely that in clinical practice the patients would be lumped into 2 categories: positive (i.e. not a surgical candidate and thus eligible for PRRT) or negative (i.e. ineligible for PRRT as the patient did not demonstrate binding to SSTR2) unless the NDA shows a significant difference in efficacy based upon the uptake seen on imaging that the sponsor and OHOP would like to be reflected in product labeling. However, the dose of drug administered in the protocols was not dependent upon the specific results of the imaging as long as uptake on the OctreoScan was >1. There was only 1 dosing regimen utilized across the protocols (7.4 Gy x 4 cycles).*
- *Therefore, the utility of the OctreoScan in the development program was to ensure that the patient's enrolled and administered the product still had SSTR2 positive tumors that would bind/take up the therapeutic product. Patients who would not be likely to see efficacy and thus did not have an acceptable risk/benefit ratio were excluded from the study based upon the OctreoScan. Review of the sponsor's proposed label does not mention imaging criteria as a determinant for therapy.*

**2. Please provide a general review of the dosimetry plan, study drug administration parameters, dose and dosing regimen for Lutathera.**

**Dosimetry Plan**

According to section 2.6 of the sponsor’s proposed labeling, there is no plan for individual patient dosimetry. The label reports the dosimetry data obtained during the drug development program.

In the NETTER-1 dosimetry substudy, one finds that there is significant interpatient variability with respect to organ doses and intrapatient variability with respect to tumor doses. Neither of these findings is surprising. The rate limiting organs appear to be predominantly bone marrow and less so the kidney particularly when an amino acid infusion is utilized. The organ doses that were found in the substudy are consistent with those in the literature.

**Table 3** Dosimetry data in 12 patients

Patient #	Injected activity (IA, GBq)	Kidney dose/IA (Gy/GBq)	Cumulative kidney dose (Gy)	Cumulative kidney BED (Gy)	Bone marrow dose/IA (Gy/GBq)	Cumulative bone marrow dose (Gy)	Liver dose/IA (Gy/GBq)	Cumulative liver dose (Gy)	Spleen dose/IA (Gy/GBq)	Cumulative spleen dose (Gy)
5	22.2	1.65	37	41	0.06	1.3	0.20	4.4	1.95	43
10	22.1	0.87	19	21	0.05	1.1	0.26	5.7	2.91	64
13	26.6	0.62	17	17	0.04	1.1	0.08	2.1	0.64	17
14	29.2	0.52	15	16	0.03	0.9	0.89	25.9	0.42	12
18	26.5	0.74	20	21	0.03	0.8	0.45	11.8	0.65	17
20	25.9	0.92	24	26	0.05	1.3	0.15	3.9	1.96	51
24	25.2	0.61	15	17	0.02	0.5	0.41	10.3	0.59	15
26	25.2	1.05	26	31	0.03	0.8	n.a.	n.a.	n.a.	n.a.
28	25.2	0.54	18	15	0.02	0.5	0.23	5.7	1.57	40
29	25.2	0.59	15	16	0.02	0.5	n.a.	n.a.	n.a.	n.a.
30	25.2	0.33	8	9	0.02	0.5	0.16	4.0	0.47	12
33	28.9	1.10	32	38	0.03	0.9	1.01	29.2	0.42	12

Patients #5, 10, 13, 14, 18 and 20 from group 1; #24, 26, 28, 29, 30 and 33 from group 2

n.a. not assessed

Due to the uncertainty in how to dose and assess toxicity of radiopharmaceuticals as well as the historical use of individual patient dosimetry in the radiation oncology clinic, dosimetry was utilized to confirm normal biodistribution and to limit radiation dose to the normal tissues. The radiation dose limits to normal, non-tumorous tissues have been co-opted from the historical experience with I-131 and external beam data e.g., 2 Gy to the marrow and 23 Gy to the kidneys. The use of dosimetry with Lutathera has been discontinued over the course of its development program given the widespread use of the product in the EU and the lack of unexpected rates of AEs. [Note that the dosimetry for another therapeutic radiopharmaceutical, Zevalin, was initially required at the time of approval and was later removed from the label.] According to the literature, the expected renal toxicity has not been seen and is not correlated with dosimetry. The rate limiting organ appears to be bone marrow.

In two reviews by Bergsma, et al assessing the toxicities (defined for renal as CTCAE v4.03 grade 3 or 4; defined for hematologic as CTCAE v3.0) of Lutathera, the authors conclude that dosimetry is unable to predict hematologic and renal toxicity. However, note that full dosimetric data was not available on all patients.

In a detailed, retrospective review of patients from the European Institute of Oncology in Milan by Bodei, et al 278 patients were treated with <sup>177</sup>Lu dotatate. The median cumulative dose was ~23 Gy and the median number of cycles was 5 (greater than the submitted trials and the proposed labeling). See table below.

Eur J Nucl Med Mol Imaging (2015) 42:5–19

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**Table 1** PRRT treatment protocols in 807 patients

Protocol		No. of patients	Cumulative activity (GBq)		No. of cycles	
			Median	Range	Median	Range
PRRT protocol (n=793)	<sup>177</sup> Lu-octreotate	278	22.9	1.7–31.8	5	1–10

Toxicity was assessed using CTCAE v4.0. Nephrotoxicity was defined as any transient or persistent elevation in creatinine (non-renal causes of creatinine elevation were excluded a priori). Median follow-up 30 months (range 1-180).

A subset of 10 patients with dosimetry was analyzed. Note the 2 cases of MDS one of which progressed to AML.

Patient no.	NET	Risk factors	Peptide	Injected activity (GBq)	Cumulative kidney dose (Gy)	Cumulative kidney BED (Gy)	Creatinine toxicity		Renal BED vs. threshold	Cumulative marrow dose (Gy)	MDS/AL	Marrow dose vs. threshold	Follow-up (months)
							Grade	Duration					
125	Ileal	Hypertension	<sup>177</sup> Lu	25.2	26.5	31.0	1	Transient	Below	0.76	No	Below	84
126	Ileal	Hypertension	<sup>177</sup> Lu	25.2	18.0	15.0	1	Transient	Below	0.50	No	Below	81
127	Ileal	None	<sup>177</sup> Lu	28.9	32.0	38.0	No		Below	0.87	No	Below	73
243	Appendix	None	<sup>177</sup> Lu	22.1	19.2	21.0	No		Below	1.10	MDS, acute myeloid leukaemia	Below	88
273	Duodenal	None	<sup>177</sup> Lu	25.9	24.0	26.0	No		Below	1.30	MDS	Below	50
440	pancreatic	None	<sup>177</sup> Lu	25.2	15.0	17.0	No		Below	0.50	No	Below	27
442	Pancreatic	None	<sup>177</sup> Lu	25.2	15.0	16.0	No		Below	0.50	No	Below	81
443	Pancreatic	None	<sup>177</sup> Lu	25.2	8.0	9.0	No		Below	0.50	No	Below	35
639	Bronchial	Diabetes	<sup>177</sup> Lu	29.2	15.0	16.0	No		Below	0.90	No	Below	104
641		None	<sup>177</sup> Lu	26.5	20.0	21.0	No		Below	0.80	No	Below	44

The following toxicity was seen in <sup>177</sup>Lu patients (N=290)

Grade CTCAE v4.0	Number renal	% renal	Number heme	% heme
0	216	74.5	23	7.9
1	69	23.8	188	64.8
2	5	1.7	70	24.1
3	0	0	9	3.1
4	0	0	0	0

Sources:

- Bergsma et al, 2016. Subacute hematotoxicity after PRRT with <sup>177</sup>Lu-DOTA-octreotate: prognostic factors, incidence and course. *Eur J Nucl Med Mol Imaging*, 43:453–463. DOI 10.1007/s00259-015-3193-4
- Bergsma et al, 2016. Nephrotoxicity after PRRT with <sup>177</sup>Lu-DOTA-octreotate. *Eur J Nucl Med Mol Imaging*, published online. DOI 10.1007/s00259-016-3382-9
- Bodei et al, 2015. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumors: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging*, 42:5-19.

- Note that Kwekkeboom is an author on these articles and that the patients from the Bergsma articles were enrolled in the Erasmus trial. It is not clear if the patients in the Bodei article participated in either of the Erasmus or netter trials.

**Reviewer comment:**

**The findings of a lack of correlation of dosimetry to toxicity may indicate that we are dosing the product incorrectly (fixed dose), that the radiation dose is too low therefore, we are not seeing the AEs that we would if it were being dosed individually for maximum efficacy if based upon some yet to be determined variable(s). [The renal toxicity of the same and similar peptides labelled with 90Y has been clearly demonstrated in the literature. 90Y delivers a larger renal dose than 177Lu.] The lack of ability of dosimetry to predict toxicity is supported by the patients who were treated on the protocol without dosimetry.**

**Study Drug administration parameters**

In the sponsor’s proposed labeling, the sponsor recommends use of an antiemetic, an amino acid infusion beginning 30 minutes prior to Lutathera administration, followed by Lutathera infusion over 30 minutes.

Product to inject	Start time (h)	Infusion rate* (mL/h)	Duration
Antiemetic	0	bolus	-
Amino acids solution, (b) (4) commercially available (1.5 L to 2.2 L)	0	250 - 550	4 hours
LUTATHERA	0.5	50	≈ 30 minutes

**Reviewer comment: This administration recommendation is consistent with the NETTER trial and the methods used in the clinics in the EU and the US.**

**Dose and dosing regimen**

Note the following:

- only 1 dose of the drug was studied
- the dose was not individualized (e.g. fixed dose not weight or BSA adjusted)
- the dose was not modified for tumor burden based upon imaging results (OctreoScan)

The dose and dosing regimens used in the studies were:

- NETTER-1:  
7.4 GBq (200 mCi) IV over 30 minutes x 4 fractions every 8 – 16 weeks = 29.6 GBq (800 mCi) total

A concomitant commercially available, locally approved parenteral amino acid solution was given for kidney protection (>36 g of lysine + arginine in <2 L, <1100 mOsm/L)

- Erasmus:

7.4 GBq (200 mCi) x 4 fractions every 6 – 13 weeks = 29.6 GBq (800 mCi) total

A locally compounded solution of amino acids was given with each administration for kidney protection (lysine <sup>(b) (4)</sup>, and arginine <sup>(b) (4)</sup>).

From the literature:

- Zaknun et al, 2013. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*, 40:800–816

*<sup>177</sup>Lu-DOTATATE / <sup>177</sup>Lu-DOTATOC*

- Administered activity: 5.55–7.4 GBq (150–200 mCi)
- Number of cycles: three to five
- Time interval between cycles: 6–12 weeks

*This is consistent with the dosing utilized by the sponsor.* <sup>(b) (4)</sup>

- Bodei et al, 2011. Peptide receptor radionuclide therapy with <sup>177</sup>Lu-DOTATATE: the IEO phase I-II study. *Eur J Nucl Med Mol Imaging*, 38:2125–2135. DOI 10.1007/s00259-011-1902-1
  - Conducted a dose escalation study from 3.7 – 7.4 GBq x ~4 cycles
  - N=51 patients
  - Dosimetric analysis performed showed cumulative renal absorbed doses ranging from 8 to 37 Gy (9–41 Gy of BED). Cumulative bone marrow doses ranged from 0.5 to 1.3 Gy.
  - No DLT. 1 patient had grade 3 leukopenia and thrombocytopenia post last cycle
  - No grade 3 or 4 renal toxicity; creatinine values increased by 30% (but remained within normal limits) at 12 months follow up; creatinine clearance ~20% decrease at 6 months, ~28% decrease at 12 months, ~28% decrease at 2 years with losses >20% in patients with hypertension or diabetes.
  - Based upon this study, 7.4 GBq x 4 cycles was considered

***Reviewer comment: It is difficult to comment on the dose because once 7.4 GBq / cycle was identified as the acceptable dose by Bodei, no further dose escalation was conducted. The dosing trend appears to be escalating the number of cycles rather than the dose / cycle as well as combining this treatment with other radiolabeled products or chemotherapy products. It can be assumed that immunotherapy will be explored in combination with this product in the future.***

**3. Please comment on the acceptability of the amino acid solutions used in the studies (Vamin 18 [EU] and Aminosyn II 10% [US]).**

The amino acid solutions are used to decrease the radiation dose to the kidney. The radiation dose to the kidney is due to uptake by the megalin/cubilin system via receptor-mediated endocytosis in the proximal tubule cells in the renal cortex. Positively charged amino acids such as lysine and arginine competitively inhibit reabsorption of Lutathera in the proximal tubules.

The NETTER dosimetry substudy did not perform the assessments with and without AA use. The Erasmus dosimetry substudy did assess 6 patients with and without AA use (only 1 solution was assessed). It is my impression that these are the same 6 patients mentioned in the Kwekkeboom article noted below.

The DMIP reviewer searched the literature for articles (yield=5) comparing kidney dosimetry with and without different amino acid solutions. If AEs were mentioned in the publications, they are noted below.

**1. Kwekkeboom et al, 2001.** [177Lu-DOTA0,Tyr3]octreotate: comparison with [111In-DTPA0]octreotide in patients. *Eur J Nucl Med* 28:1319–1325.  
DOI 10.1007/s002590100574

- Not designed to assess AA solutions but did assess change in kidney dose
- <sup>177</sup>Lu DOTATATE (1850 MBq or about 50 mCi)
- N = 6; 5 patients with and without AA infusion
- Only 1 AA solution utilized: lysine 2.5%, arginine 2.5% in 1 L 0.9% NaCl
- Biodistribution was comparable to octreoscan
- Tumor uptake and retention were higher than octreoscan
- Used maximum cumulative dose of 23 Gy to kidneys to calculate potential dose
  - Possibly the basis for the current dosing of 7.9 Gy x 4 fractions
- Did not mention AEs
- See table below for decrease in kidney dose seen with use of AA.

**Table 1.** Patient organ doses in cGy

Patient	Kidneys	
	Without AA	With AA
1	825	403
2	533	–
3	692	282
4	359	252
5	648	366
Mean	611	326

**2. Bodei et al, 2003.** Receptor-mediated radionuclide therapy with 90Y-DOTATOC in association with amino acid infusion: a phase I study. *Eur J Nucl Med* 30:207–216.  
DOI 10.1007/s00259-002-1023-y

- Design:

- 90Y DOTATOC
- N = 40 patients with SSTR2 + tumors
- AA solution – see table 2 below

Table 2. Amino acid administration protocols in three different groups of patients: dosage and side-effects

Group	Amino acid pre therapy	Amino acid post therapy	G.I. toxicity <sup>a</sup> (grade I/II-NCI)
I (L.A.; 16 pts)	20 g lysine in 1,000 ml + 40 g arginine in 1,000 ml over 3–4 h before therapy	–	11/16 (69%)
II (L.A.L.; 14 pts)	10 g lysine in 500 ml + 20 g arginine in 500 ml over 1–2 h before therapy	10 g lysine in 500 ml over 2–3 h after therapy	7/14 (50%)
III (L.L.; 10 pts)	10 g lysine in 500 ml over 1 h before therapy	15 g lysine in 750 ml over 2 h after therapy	1/10 (10%)

NCI, National Cancer Institute Common Toxicity Criteria

<sup>a</sup>Nausea and vomiting

Note that these are unique solutions compared to the 25 g each lys/arg typically utilized in the following publications.

AEs were fewest with group III.

Table 3. Intra-patient comparative dosimetric study after <sup>90</sup>Y-DOTATOC. Each patient underwent two dosimetric estimates with and without amino acid infusion using <sup>111</sup>In-DOTATOC. Significant reduction was noted mainly in the kidneys and spleen

Patient no.	Amino acid infusion <sup>a</sup>	Absorbed doses (mGy/MBq)	
		Kidneys	Reduction in kidney dose
4	Basal	5.7	
	L.A.	4.6	19%
16 <sup>b</sup>	Basal	5.3	
	L.A.	4.2	21%
22	Basal	3.7	
	L.A.L.	3.0	18%
29	Basal	4.8	
	L.A.L.	3.3	32%
33	Basal	2.9	
	L.L.	2.3	23%
38	Basal	4.3	
	L.L.	3.2	26%

<sup>a</sup> See Materials and methods and Table 2 for details

<sup>b</sup> See also Fig. 1b

Reduction in kidney dose from with amino acid administration was within the 20%–30% range.

**3. Jamar et al, 2003.** A phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. *EJNMMI* 30:510–518. DOI 10.1007/s00259-003-1117-1

- Design: phase 1, single-center, open label, cross-over study to evaluate the renal protective effects of AA infusions
- <sup>86</sup>Y DOTA0-D-Phe1-Tyr3-octreotide (SMT487 aka DotaTOC)
  - <sup>86</sup>Y is a surrogate for <sup>90</sup>Y
- N=24 with NETs and positive OctreoScan scintigraphy

- Five regimens were tested on an intra-patient basis
  - No solution
  - 4-h infusion of 120 g mixed AA (26.4 g L-lysine + L-arginine)
  - 4 h L-lysine (50 g)
  - 10 h 240 g mixed AA (52.8 g L-lysine + L-arginine)
  - 4 h Lys-Arg (25 g each)
- Results
  - Any AA mixture was better than none
    - The maximum allowed dose [MAD = the amount of <sup>90</sup>Y-SMT487 that would result in the 23 Gy cut-off dose to kidneys] was higher by a mean of 46% with 4 h AA than without infusion
    - Did not inhibit tumor uptake
    - Decreased kidney uptake resulting in decreased radiation dose
  - 4 h Lys-Arg (25 g each) is probably the best option based upon
    - MAD – allowed was > by a mean of 16% compared to 4 h AA
    - Potentially less nausea, vomiting, dizziness; logistics 10 h vs. 4 h

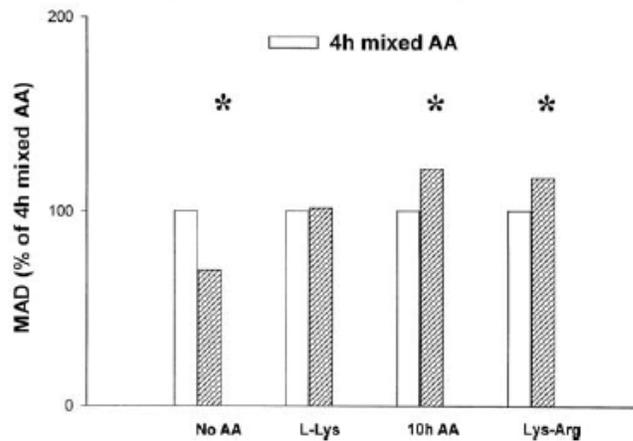


Fig. 5. Comparison of the maximal allowed dose (MAD, i.e. a dose of <sup>90</sup>Y-SMT487 that would result in a 23 Gy radiation dose to kidneys). To allow inter-cohort comparisons, data were normalised to 100% corresponding to the MAD with a 4-h mixed AA infusion. The lowest MAD was reached without infusion and the highest activity was achieved with a 10-h mixed AA infusion (\* $P < 0.05$  vs mixed AA)

- AEs – no specifics given only the general statements below
  - dizziness, nausea and sometimes vomiting mainly observed with mixed AA
  - transient hyperkalemia with the L-lysine and Lys-Arg infusions

**4. Rolleman et al, 2003.** Safe and effective inhibition of renal uptake of radiolabelled Octreotide by a combination of lysine and arginine. *Eur J Nucl Med* 30:9–15  
DOI 10.1007/s00259-002-0982-3

- Design – single center, open label, non-randomized, intra-patient comparison with and without AA infusion
- <sup>111</sup>In-DTPA0 octreotide
- N = 26 patients with NET

- Five regimens + control were tested on an intra-patient basis using 4 hour infusions
  - Control: saline 0.45%/glucose 2.5%
  - Commercially available AA solution (10.32 g lysine + 16.08 g arginine)
  - Lysine 25 g
  - Lysine 50 g
  - Lysine 75 g
  - Lys-Arg (25 g each)
- Results
  - Any AA mixture was better than control
  - AA mixture or Lysine 25 g: ~20% decrease kidney dose
  - Lysine 50 g did not provide additional benefit over above bullet
  - Lysine 75 g: ~ 44%±11%
  - Lys-Arg (25 g each): ~33% (P<0.01 vs control, NS vs 75 g of lysine)
- AEs
  - Nausea, vomiting – see table below – less with LysArg

Table 1. Rate of vomiting during scintigraphy or PRRT with radiolabelled octreotide, with or without concomitant infusion of different amino acid solutions

	Dose and radionuclide administered	No. of patients	Vomiting in:	
			Patients	Treatments
Control	7–10 GBq [ <sup>111</sup> In-DTPA <sup>0</sup> ]-octreotide	8		3/52 (6%)
AA	7–10 GBq [ <sup>111</sup> In-DTPA <sup>0</sup> ]-octreotide	8	4/8 (50%)	
Lys25 or Lys 50	7–10 GBq [ <sup>111</sup> In-DTPA <sup>0</sup> ]-octreotide	8		3/22 (9%)
LysArg	220 MBq [ <sup>111</sup> In-DTPA <sup>0</sup> ]-octreotide	11	1 (9%) <sup>a</sup>	NDR

<sup>a</sup> This patient had a subfebrile temperature, malaise and nausea before the first treatment. During this treatment she vomited twice, probably due to tumour necrosis. No problems occurred during five later infusions

- K<sup>+</sup> concentrations were higher with 75 g of lysine than with LysArg
    - LysArg: K<sup>+</sup> = 6.0 mmol/l in one patient
    - 75 g Lysine: 3/6 patients K<sup>+</sup> = 6.3, 6.7 and 6.8 mmol/l.
- Best option: most likely Lys-Arg 25 g each based upon:
  - decreased kidney dose
  - fewer AEs.

**5. Zaknun, et al, 2013.** The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 40:800–816. DOI 10.1007/s00259-012-2330-6

- (b) (4)
- positively charged amino acids competitively inhibit the proximal tubular reabsorption of the radiopeptide
- reduction in the renal absorbed dose ranges from 9 % to 53 %
  - Renal absorbed dose is further reduced by up to 39 % by extending the infusion time of the AA solution over 10 h, and up to 65 % by extending the protection over 2 days post radiopeptide administration
- Recommended 1 day protocol

- 50-g cocktail of lysine and arginine (25 g of lysine and 25 g of arginine) diluted in 2 liters of normal saline infused over 4 h, starting 30–60 min before PRRNT.

The sponsor submitted the following table (see below) comparing the amino acid solutions utilized in their submitted trials.

**Table 1: Composition of amino acid solutions used in clinical studies**

Study	NETTER-1		Erasmus MC Study
Clinical site location	US	EU	The Netherlands
Solution name	Aminosyn II 10% sulfite free	Vamin 18	Customized solution manufactured by (b) (4)
SmPC/PI date	Nov-2010	June-2008	NA
Amino acid formula (g/L)			
	(b) (4)		
<b>Arginine</b>	(b) (4)		
	(b) (4)		
<b>Lysine</b>	(b) (4)		
	(b) (4)		
	(b) (4)		



The sponsor’s proposed labeling submitted in the NDA states the need for the use of an AA solution (b) (4). The proposed label also describes the specifications of commercially available amino acid solution that would be sufficient alternatives. These appear to be consistent with the AA solutions used in the publications above.

Item	Specification
Lysine HCl content	Between 18 and 24 g
Arginine HCl content	Between 18 and 24 g

One notes that the publications above state that the amino acid solutions have AEs such as nausea, vomiting, and hyperkalemia.

- The label comments on the need for antiemetics to address the GI AEs however, it does not mention the need for monitoring for hyperkalemia during the AA infusion. **OHOP may wish to ask the sponsor to add this information to the label.**
- The AEs appear to be less when the lysine/arginine combination is utilized rather than the commercial products.

*Overall, based upon the information available in the literature it can be concluded that:*

- *Use of any AA solution containing positively charged lysine and/or arginine results in a decrease renal dose compared to no AA solution.*
- *The decrease in renal dose varies but it is reasonable to expect ~20-33% reduction.*
- *The (b) (4) g each of lysine/arginine has the least amount of nausea and vomiting but patients should be monitored for hyperkalemia.*
- *This reviewer agrees with the recommendation in the label of use of an AA solution consisting of lysine/arginine ( (b) (4) g each) IV over 4 hours beginning 30 minutes prior to injection of the therapeutic radioisotope.*

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**4. Please provide any additional comments/concerns you may have with the data submitted in the application.**

- Ranade and Basu, 2016. 177Lu-DOTATATE PRRT in Patients with Metastatic Neuroendocrine Tumor and a **Single Functioning Kidney**: Tolerability and Effect on Renal Function. *J Nuc Med Technol*, Jun;44(2):65-9. doi:10.2967/jnmt.115.168146. Abstract only available.
  - Retrospective
  - N=6 patients with a single functioning kidney who had grade 3 uptake on imaging scan and received 3-5 cycles 177Lu Dotatate with cumulative doses of 16-36 GBq
  - Follow up 12-56 months
  - CTCAE v4.0

- All patients with overall chronic renal toxicity showed compromised renal function at baseline. Only 2 patients showed a reduction in GFR (5.3% in one and 13.84% in the other). Four patients showed a reduction in Effective Renal Plasma Flow (31.4% in the patient with the greatest reduction), and all had a rise in filtration fraction signifying that tubular parameters were more affected than glomerular parameters.
- Basu et al, 2016. Metastatic Neuroendocrine Tumor with **Extensive Bone Marrow Involvement at Diagnosis**: Evaluation of Response and Hematological Toxicity Profile of PRRT with <sup>177</sup>Lu-DOTATATE. *World J Nucl Med*, Jan-Apr; 15(1): 38–43. doi:10.4103/1450-1147.165353
  - Retrospective
  - N= 5 patients with diffuse bone marrow metastases who had grade 3 uptake on imaging scan and received 3 cycles <sup>177</sup>Lu Dotatate with cumulative doses of 16-25 GBq (1 patient received 4 cycles)
  - Follow up 10-27 months
  - CTCAE v4.0
  - Patient 2 had baseline anemia that persisted throughout treatment (14.9 GBq total cumulative dose)
  - No other hematologic toxicity noted

***Reviewer comment: Despite the limitations of these retrospective articles, they provide some preliminary support for use of this product in patients with extensive marrow disease or diminished renal capacity.***

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/s/  
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CYNTHIA A WELSH  
08/18/2016

ALEXANDER GOROVETS  
08/18/2016

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>IND or NDA</b>	NDA 208700
<b>Brand Name</b>	Lutathera®
<b>Generic Name</b>	<sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate
<b>Sponsor</b>	Advanced Accelerator Applications USA, Inc.
<b>Indication</b>	Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults
<b>Dosage Form</b>	Solution for intravenous infusion (IV)
<b>Drug Class</b>	Radiopharmaceutical
<b>Therapeutic Dosing Regimen</b>	4 administrations of 7.4 GBq (200 mCi), at 8 week intervals
<b>Duration of Therapeutic Use</b>	Acute
<b>Maximum Tolerated Dose</b>	Not determined
<b>Submission Number and Date</b>	SDN 003; 28 Apr 2016
<b>Review Division</b>	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

Although a large change (i.e., >20 ms) in QTc interval was not detected in this ECG sub-study for Lutathera (<sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate), mean changes above 10 ms were observed at 8 hours and 24 hours post-dosing. Placebo control and ECG positive control were not included in the sub-study.

A heart rate increasing effect was observed. The mean change from baseline in HR ( $\Delta$ HR) peaked at 8 hours post the end of infusion with  $\Delta$ HR value of 18.7 bpm (90% CI: 12.4 to 25.0 bpm).

In this ECG sub-study conducted within on-going Phase III study NETTER-1 (multicenter, stratified, open, randomized, and comparator-controlled parallel-group study), 20 patients with inoperable, progressive, and somatostatin receptor positive midgut carcinoid tumors enrolled in the sub-study and received Lutathera. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs corresponding to the Largest Upper Bounds for Lutathera (FDA analysis)**

Time (Hour)	$\Delta$ QTcF (ms)			
	N	LSMean	SE	90% CI
24 Hour after the End of Infusion (EOI)	16	11.3	3.2	(5.7, 16.9)

The maximum mean increase in QTc did not coincide with the  $T_{max}$  values for Lutathera, but occurred at the later time point of 24 hours, suggesting delayed effect of QTc prolongation with Lutathera treatment. Further prolongation beyond 24 hours cannot be ruled out with the current data. Given the delayed effect, the concentration-QTc analysis conducted by the sponsor is not considered reliable.

## 2 PROPOSED LABEL

*The sponsor did not propose any clinical QT labeling language. QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.*

### 12.2. Pharmacodynamics

#### Cardiac Electrophysiology

The <sup>(b) (4)</sup> of LUTATHERA to prolong the QTc interval at the therapeutic dose was assessed in an open label, <sup>(b) (4)</sup> study in 20 patients with <sup>(b) (4)</sup> somatostatin receptor positive midgut carcinoid tumors. <sup>(b) (4)</sup>

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

<sup>(b) (4)</sup>

*Source: Applicant's annotated PI, Section 11 and 12*

### 3.2 MARKET APPROVAL STATUS

Lutathera is not approved for marketing in any country.

### 3.3 PRECLINICAL INFORMATION

The possible effects of  $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  formulation on hERG tail current have been tested in vitro in HEK-293 cells stably transfected with hERG-1 cDNA. No relevant effects of the compound on the hERG tail current have been observed, indicating no particular potential for the compound to cause prolongation of the cardiac action potential or increase of QT interval. The absence of any effect on the cardiac conduction times was also confirmed in the in vivo study in Beagle dogs, in which the effects of  $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  on blood pressure, heart rate, body temperature and electrocardiogram (duration of PR, PQ, QT and QRS) after single i.v. administration were investigated. The results of this study showed that the compound does not have any effect on cardiac conduction times or body temperature, and does not cause arrhythmia at the doses tested (from 80 up to 800  $\mu\text{g}/\text{kg}$ , that is 10 to 100 fold the intended human dose, scaled to dog based on body surface area), indicating that the compound does not have any effect on the cardiac conduction tissue.  $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  showed to have a hypertensive effect associated with a reflex mediated bradycardia when administered intravenously, either as bolus (80, 250 and 800  $\mu\text{g}/\text{kg}$ ) or slow infusion (40  $\mu\text{g}/\text{kg}$  and 80  $\mu\text{g}/\text{kg}$ ).

*Source: Highlights of Clinical Pharmacology*

*Reviewer's Comments:  $^{175}\text{Lu-DOTATATE}$  is the non-radioactive compound.*

### 3.4 PREVIOUS CLINICAL EXPERIENCE

Here is the excerpt about the safety in the Phase 3 NETTER-1 trial and pooled data from Phase 1/2 Erasmus MC and the Phase 3 NETTER-1 trial:

In a sub-study to the phase III trial NETTER-1, 20 subjects underwent serial PK and ECG assessment, and results were assessed using exposure response (ER) analysis. ECGs were measured at a central ECG laboratory (b) (4), at which the ER analysis was also performed. The ER analysis demonstrated a very shallow and statistically significant slope of the relationship between the  $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  decay corrected activity concentrations and the effect on the QTc interval: -0.009 msec; 90% CI: -0.016 to -0.002. The predicted  $\Delta\text{QTcF}$  effect using ER analysis was 0.98 msec (90% CI: -2.77 to 4.74) at the observed geometric mean peak decay corrected activity level (402 kBq/ml) after dosing with  $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ , which is consistent with the small changes observed at individual timepoints, post-dosing.  $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  did not have any effect on cardiac conduction (PR and QRS intervals).

When assessing the NETTER-1 Phase III randomized controlled study adverse events alone, no cases of torsade de pointes, seizure or ventricular tachycardia, fibrillation or flutter were reported. Two cases of prolonged QT interval were reported in Lutathera arm (2%) vs. 1 in control arm (1%). One of those cases was reported as related to Lutathera according the investigator. In the Sponsor's view the main culprit in triggering the repeated acute episodes of QTc prolongation could be ondansetron medication, with a background contribution of an underlying predisposition (medical history of heart disease and chronic medication with anxiolytic: delorazepam).

The incidence of syncope was also higher in Lutathera arm (5%, 3% when considering only the grade 3 or 4) than in the control arm (2%, 1%). The most relevant serious cases which could be linked with cardiac outward signs were:

One 62-year old female patient who experienced a second degree atrioventricular block and syncope which led to pacemaker insertion due to risk of sudden cardiac death. According to the Investigator, a worsening of the underlying atrioventricular block had occurred after investigational treatment start. This event can also be related to known patient's risk factors (hypertension and type 2 diabetes mellitus), however, the relationship with Lutathera administration protocol cannot be totally excluded. A role of concomitant amino acid infusion seems more likely (through hyperkalemia commonly reported during amino acid infusion) than a role of Lutathera itself. However, blood potassium at time of events was not available, thus the available data do not allow validating this hypothesis.

One 66-year old male patient who experienced a syncope episode followed by hospitalization because of disease aggravation and then sudden cardiac arrest leading to death. According to investigator the event was not related to study drug. The root etiology of the sudden chain of events was most probably the underlying malignancy (either tumor bleeding into the gastro-intestinal tract or tumor erosion into blood vessels) and its secondary and tertiary complications (state of shock that was multifactorial - hypovolemic / hemorrhagic, septic...), although comorbid events such as gastroesophageal reflux disease aspirations may have surely contributed.

Of note, in this study incidence of atrial fibrillation was higher in the Lutathera arm 4% (all of grades 1 or 2) than in the control arm (0%).

From the pooled analysis of Integrated Summary of Safety (n = 921 patients treated with  $^{175}\text{Lu-DO}^0\text{-Tyr}^3\text{- Octreotate}$  from the Erasmus MC Phase I/II and the NETTER-1 Phase III studies) the incidence of serious adverse events of interest for assessing drug proarrhythmic potential was limited. No cases of torsade de pointes, seizure or ventricular fibrillation or flutter were reported. Two cases (0.2% of patients) of sinus tachycardia and 1 case (0.1%) of tachycardia of unspecified origin were reported, but no cases of ventricular tachycardia were observed. Six cases (0.7%) of syncope were reported which however could not be formally attributed to cardiac events except for the patients from the NETTER-1 study mentioned above.

*Source: Highlights of Clinical Pharmacology*

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of Lutathera's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report AAA-III-01 for Lutathera, including electronic datasets and waveforms to the ECG warehouse.

## **4.2 TQT STUDY**

### **4.2.1 Title**

On-going Phase III study NETTER-1:

A Multicenter, Stratified, Open, Randomized, Comparator-Controlled, Parallel-Group, Phase III Study Comparing Treatment with  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate to Octreotide LAR in Patients with Inoperable, Progressive, Somatostatin Receptor Positive, Midgut Carcinoid Tumours

### **4.2.2 Protocol Number**

Protocol number of the ECG sub-study within Phase III study NETTER-1: AAA-III-01

### **4.2.3 Study Dates**

ECG sub-study AAA-III-01 was conducted within on-going Phase III study NETTER-1. Cardiac safety report for study AAA-III-01 was dated 31 Mar 2016.

### **4.2.4 Objectives**

The primary objective of the ECG sub-study was to evaluate the effect of Lutathera on cardiac repolarization as measured by the QTcF interval in the enrolled subjects.

The secondary objective of the ECG sub-study was to evaluate the effect of Lutathera on other ECG parameters.

### **4.2.5 Study Description**

#### **4.2.5.1 Design**

Phase III study NETTER-1 was an open-label, randomized, comparator-controlled, parallel-group study. ECG sub-study AAA-III-01 within study NETTER-1 was conducted in patients receiving Lutathera.

#### **4.2.5.2 Controls**

There were no placebo and positive (moxifloxacin) controls.

#### **4.2.5.3 Blinding**

The study was open-label.

### **4.2.6 Treatment Regimen**

#### **4.2.6.1 Treatment Arms**

For patients treated with Lutathera, 4 intravenous infusions (cumulative amount of radioactivity of 29.6 GBq) were administered at 8-week intervals or up to 16 weeks to accommodate resolving acute toxicity of radioactivity. Each intravenous infusion of Lutathera was administered over 30 minutes.

In addition to treatment with  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate, subjects received 30 mg Sandostatin<sup>®</sup> LAR Depot every 4 weeks until the PFS Primary End-Point, then until Week 72 from randomization after the PFS Primary End-Point, or early termination, unless the subject progressed or died. Sandostatin<sup>®</sup> LAR Depot was not administered until at least 5 hours post  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate infusion. Sandostatin<sup>®</sup> LAR was not used within 4 weeks of  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate administration. During this period daily injections of Sandostatin<sup>®</sup> s.c. were allowed, except within 24 hours of PRRT treatment.

On the day of  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate treatment and before the infusion with amino acids was started, an intravenous bolus of anti-emetic was given.

The amino acid solution and  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate (22-25 mL) were administered in parallel by peripheral vein infusion in one arm at a constant infusion rate through pumps or any other infusion system. The infusion with amino acids was started 30 minutes before the start of the  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate infusion, and continued for a total of 4 hours.

#### 4.2.6.2 Sponsor's Justification for Doses

No increase in exposure above the range determined in the Dosimetry, Pharmacokinetic and ECG sub-study of the NETTER-1 Phase III study is expected, based on the following:

- the dose in terms of radioactivity is precisely defined and measured before administration.
- it is given intravenously, so absorption variability is not a factor that could have an impact on exposure.
- treatment regimen consists in 4 administrations spaced by 8 week interval, so no accumulation is expected.
- renal function must meet pre-defined criteria for the patient to be eligible for treatment with Lutathera, and therefore no relevant differences in renal elimination are expected
- no evidence was found regarding compound metabolization. Therefore, no impact on compound fate due to possible metabolic differences is expected.

*Reviewer's Comment: Acceptable. The dose studied in this sub-study is the clinical therapeutic dose.*

#### 4.2.6.3 Instructions with Regard to Meals

Not applicable.

*Reviewer's Comment: There is no necessity of instructions with regard to meals, since the drug is to be administered as an IV infusion.*

#### 4.2.6.4 ECG and PK Assessments

ECG: Replicate ECGs (up to 10) were extracted from the continuous digital 12-lead ECG recording at pre-dose, middle of infusion, end of infusion, then after the end of infusion: 20 min, 40 min, 1 hour, 2 hour, 4 hour, 8 hour, and 24 hour.

PK: Sampling was done to match the time points in ECG sampling.

*Reviewer's Comment: The  $T_{max}$  for Lutathera is around the time of end-of-infusion (Refer Figure 5). The time was covered by the selected time points for PK and ECG measurements for assessing direct effect of concentration on QTc prolongation. However, there appears to be a delayed effect of QTc prolongation with Lutathera treatment with maximal effect at the last assessed time point of 24 hours and further prolongation beyond 24 hours cannot be ruled out with the current data.*

#### **4.2.6.5 Baseline**

The average of pre-dose QT/QTc value was used as baseline.

#### **4.2.7 ECG Collection**

Continuous digital 12-Lead ECGs were obtained while subjects were resting. Up to 10 replicates at each time point were extracted with TQT Plus methods. Median value of acceptable beats from each extracted replicate was calculated, and then the mean of all available medians from a nominal time point was used as the reported QT/QTc value.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

A total of 20 patients with inoperable, progressive, and somatostatin receptor positive midgut carcinoid tumors enrolled in the ECG sub-study.

Of the 20 subjects enrolled, 18 were included in the timepoint level analysis. Two subjects were excluded from the timepoint level analysis due to no ECG data available for one and no pre-dose timepoint for the other, respectively.

Of the 20 subjects, 17 were included in the Concentration Effect modeling. Three subjects were excluded from the Concentration Effect modeling. One subject had concentration data deemed unreliable and therefore was excluded. The same two subjects excluded from timepoint level analysis as noted above were also excluded from the Concentration Effect modeling.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

The sponsor's results for primary analysis are displayed in the following Table 2.

Change-from-baseline QTcF ( $\Delta$ QTcF) during the treatment was small with slightly negative mean values in the middle of and at the end of the infusion (-4.0 msec and -3.8 msec, respectively). During the first two hours after the end of the infusion, mean  $\Delta$ QTcF remained very small with values below 2.8 msec, whereas the change was larger from 4 hours after the end of infusion and on-wards with mean  $\Delta$ QTcF between 4.2 msec and 11.1 msec at 4, 8, and 24 hours. Near the start and end of the infusion of amino acids (30 minutes and 4 hours, respectively), mean  $\Delta$ QTcF was -- 0.6 msec (at 40 minutes) and 4.2 msec, respectively.

**Table 2: Change from Time-matched Baseline across Timepoints for QTcF (Sponsor's Results from Statistical Modeling)**

Parameter (unit)	Time	Statistics	Value
ΔQTcF (msec)	Middle of Infusion	n	18
		LSMean	-4.0
		SE	1.5
		90% CI	(-6.6; -1.4)
	End of Infusion	n	18
		LSMean	-3.8
		SE	2.3
		90% CI	(-7.9; 0.2)
	20min Postdose	n	15
		LSMean	-2.0
		SE	1.9
		90% CI	(-5.3; 1.3)
	40min Postdose	n	16
		LSMean	-0.6
		SE	2.8
		90% CI	(-5.5; 4.2)
	1Hr Postdose	n	17
		LSMean	0.8
		SE	2.3
		90% CI	(-3.2; 4.8)
	2Hr Postdose	n	18
		LSMean	2.8
		SE	2.5
		90% CI	(-1.5; 7.2)
4Hr Postdose	n	17	
	LSMean	4.2	
	SE	3.8	
	90% CI	(-2.5; 11.0)	
8Hr Postdose	n	17	
	LSMean	10.0	
	SE	3.4	
	90% CI	(4.0; 15.9)	
24Hr Postdose	n	16	
	LSMean	11.1	
	SE	3.2	
	90% CI	(5.3; 16.8)	

Source: (b) (4) report, Table 14.3-1.3, page 15

Reviewer's Comments: Please see the reviewer's analysis in section 5.2.

#### 4.2.8.2.2 Assay Sensitivity

Not Applicable.

#### 4.2.8.2.3 *Categorical Analysis*

There was one subject with a QTcF value exceeding 450 msec at 4 timepoints and three subjects with  $\Delta$ QTcF > 30 msec at a total of 4 timepoints. No subject had a QTcF value exceeding 480 msec or  $\Delta$ QTcF > 60 msec.

#### 4.2.8.3 *Safety Analysis*

Not reported in the ECG sub-study. Please refer to clinical study report of study NETTER-1 for the safety profile of Lutathera.

#### 4.2.8.4 *Clinical Pharmacology*

##### 4.2.8.4.1 *Pharmacokinetic Analysis*

This is not included in the submission.

There was no suprathreshold dose of Lutathera utilized in the study. The concentration (decay corrected activity concentration)-time profile of therapeutic dose of Lutathera is illustrated in Figure 5 as a part of reviewers' assessment.

##### 4.2.8.4.2 *Exposure-Response Analysis*

The Applicant's concentration-QTc analysis was based on the PK/QTc population. The relationship between  $\Delta$ QTcF and  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  decay corrected activity concentrations was investigated by a linear mixed-effects modeling approach, that is,

$$\Delta\text{QTcF}_{ij} = \text{Intercept}_i + \text{slope}_i \times \text{Conc}_{ij} + \varepsilon_{ij},$$

where  $\Delta\text{QTcF}_{ij}$  was the change-from-baseline for QTcF for subject  $i$  at time  $j$  with concentration  $\text{Conc}_{ij}$ . The residual  $\varepsilon_{ij}$  was assumed to be identical, independent, normally distributed (iidN) with mean 0 and variance  $\sigma^2$ .

Three models were considered:

1. Model 1 was a linear model with an intercept [i.e.,  $\text{Intercept}_i$  was assumed to be iidN( $A, \sigma_A^2$ ) and  $\text{Slope}_i$  was iidN( $B, \sigma_B^2$ )].
2. Model 2 was a linear model with mean intercept fixed to 0 (with variability) [i.e.,  $\text{Intercept}_i \sim \text{iidN}(0, \sigma_A^2)$  and  $\text{Slope}_i \sim \text{iidN}(B, \sigma_B^2)$ ].
3. Model 3 was a linear model with no intercept [i.e., a linear model with only slope and  $\text{Slope}_i$  was assumed to be iidN( $B, \sigma_B^2$ )].

Decay corrected activity concentration was included in the model as a covariate and subject as a random effect for both intercept and slope, whenever applicable. However, when the analysis was performed the models did not converge when subject was included as a random effect for slope, therefore subject was only included as a random effect for the intercept, wherever applicable.

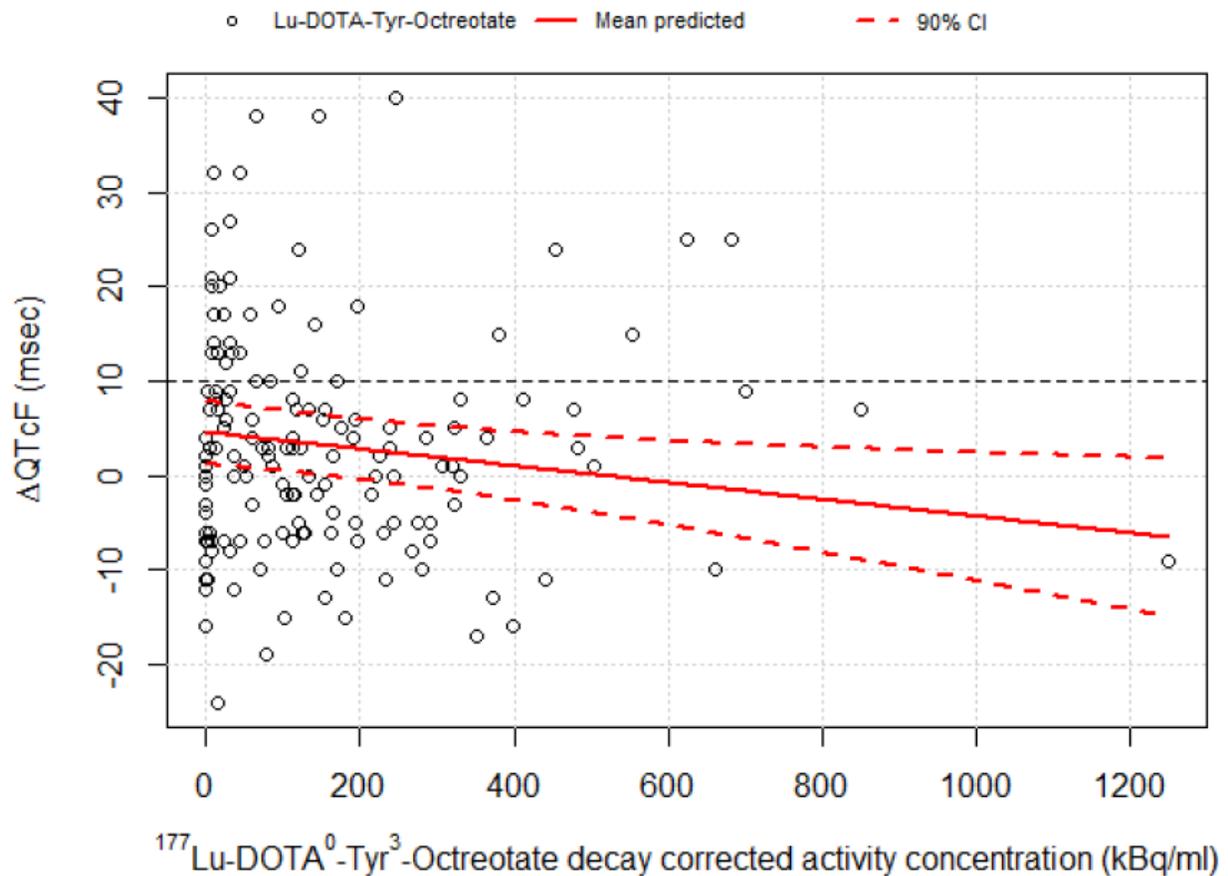
A plot of standardized residuals versus fitted values was used to examine departure from model assumptions. The normal Q-Q plots of the random effects and the within-subject errors were used to investigate the normality of the random effects and the within-subject errors,

respectively. A final assessment of the adequacy of the linear mixed effects model was provided by a goodness-of-fit plot (i.e., the observed concentration decile- $\Delta$ QTcF plot) that was proposed by the FDA's Interdisciplinary Review Team. Via visual inspection of the goodness-of-fit plot, the assumption of linearity between  $\Delta$ QTcF and decay corrected activity concentrations of  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  and how well the predicted  $\Delta$ QTcF matched the observed data in the regions of interest were checked. The goodness-of-fit plot was generated by binning the independent variable (i.e., concentrations) into deciles. The mean  $\Delta$ QTcF with 90% CI within each decile was computed and plotted at the corresponding median concentration within the decile. The decile ranges were added to the bottom of the graphs to illustrate the span of each decile and possible skewness of the tails.

The model that fit the data best (i.e., had the smallest AIC and the model predicted CIs similar to the observed CIs) was used for predicting  $\Delta$ QTcF at the geometric mean peak of methylthioninium chloride. Since  $C_{\text{max}}$  is usually log-normally distributed, the geometric mean is more appropriate to use than the arithmetic mean.

The relationship between the individually observed  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  decay corrected radioactivity concentrations and  $\Delta$ QTcF is visualized in Figure 1.

**Figure 1: Relationship between  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  decay corrected radioactivity concentrations and  $\Delta\text{QTcF}$  with 90% CI (based on Model 1)**

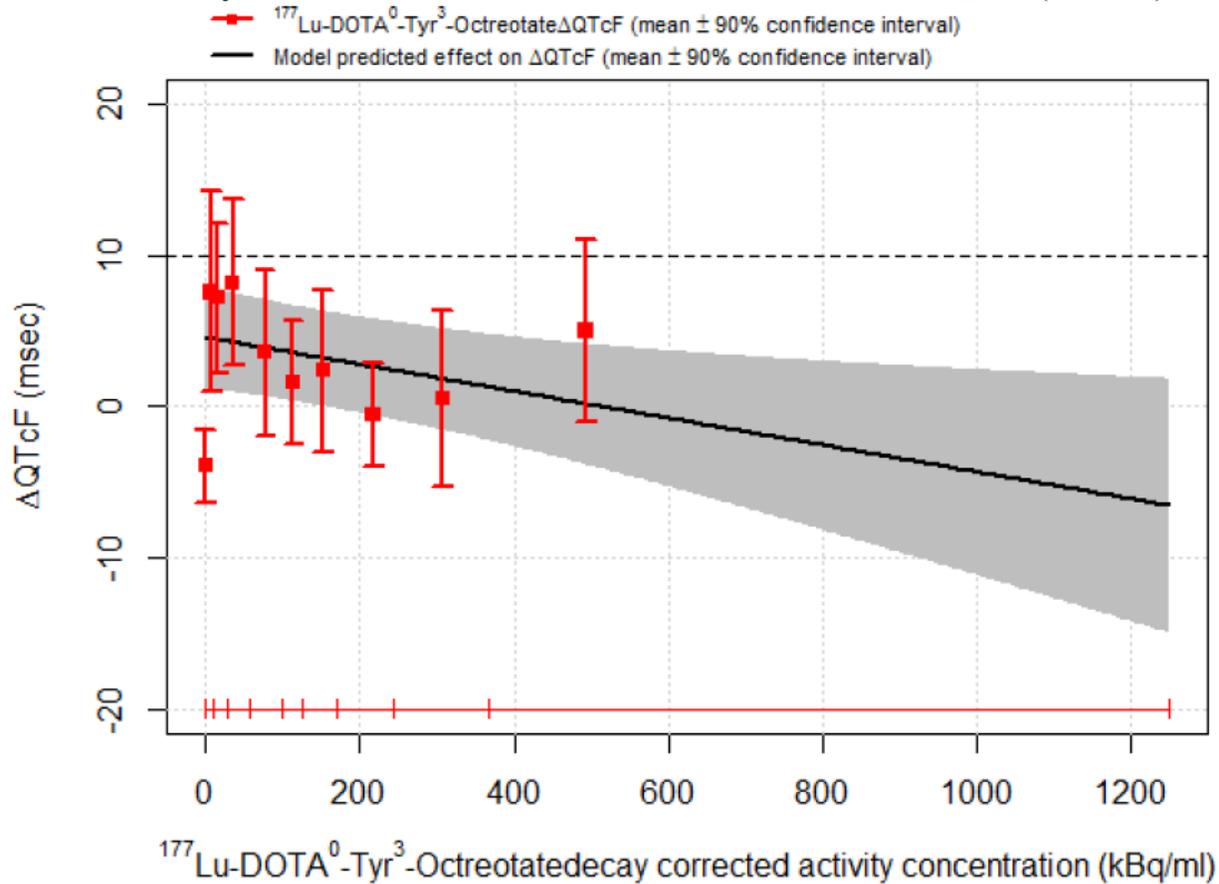


Source: (b) (4) report, Figure 14.3-2.9, page 18

Model 1 was used for further analysis since the model with an intercept was found to fit the data best (i.e., had the smallest AIC among the three candidate models).

A final assessment of the adequacy of the linear mixed effects model is given by the goodness-of-fit plot in Figure 2, which shows the mean  $\Delta\text{QTcF}$  (90% CI) within each  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  decay corrected activity concentration decile and the model-predicted mean  $\Delta\text{QTcF}$  with 90% CI. From the plot, it can be seen that the predicted  $\Delta\text{QTcF}$  values are close to the observed values. Therefore, it can be concluded that Model 1 provides a reasonable representation of the relationship between  $\Delta\text{QTcF}$  (change-from-baseline for QTcF) and  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  concentrations.

**Figure 2: Model predicted  $\Delta$ QTcF (mean and 90% CI) and observed median decile  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  concentrations with associated mean  $\Delta$ QTcF (90% CI)**



Source: (b) (4) report, Figure 14.3-2.9.4, page 20

The Table 3 summarizes the results of  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$   $\Delta$ QTcF analyses. The estimated population slope of the exposure response relationship was -0.009 msec per kBq/mL (90% CI: -0.016 to -0.002) with an intercept of 4.6 msec. The slope of the relationship was statistically significant and a slightly negative concentration-dependent effect of  $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$  on QTcF was identified.

**Table 3: Exposure-Response Analysis of <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate Associated ΔQTcF prolongation\* (Model 1 results)**

Parameter	Estimate	P-value	Between-subject Variation
ΔQTcF=Intercept + slope* <sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate concentration			
Intercept (ms)	4.556 (1.047; 8.065)	0.0366	7.330
Slope (ms per kBq/mL)	-0.009 (-0.016; -0.002)	0.0411	.
Residual Variability (ms)	9.250		

\*Model failed to converge when Subject was included as a random effect for slope.

Source: Adapted from (b) (4) report, Table 14.3-1.10, page 19

The predicted ΔQTcF at the geometric mean peak <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate decay corrected activity concentration is shown in Table 4.

**Table 4: Predicted ΔQTcF interval at geometric mean peak <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate concentration (Model 1 results)**

Treatment	Geometric Mean (90% CI) of C <sub>max</sub> (kBq/ml)	Predicted ΔQTcF (msec)	90% CI of QTcF (msec)
<sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate	401.59 (320.05; 503.91)	0.98	(-2.77; 4.74)

\* Prediction was based on Model 1. The 90% CI of the geometric mean was calculated in the logarithmic domain and presented after back-transformation to the original concentration domain.

Source: (b) (4) report, Table 14.3-1.11, page 21

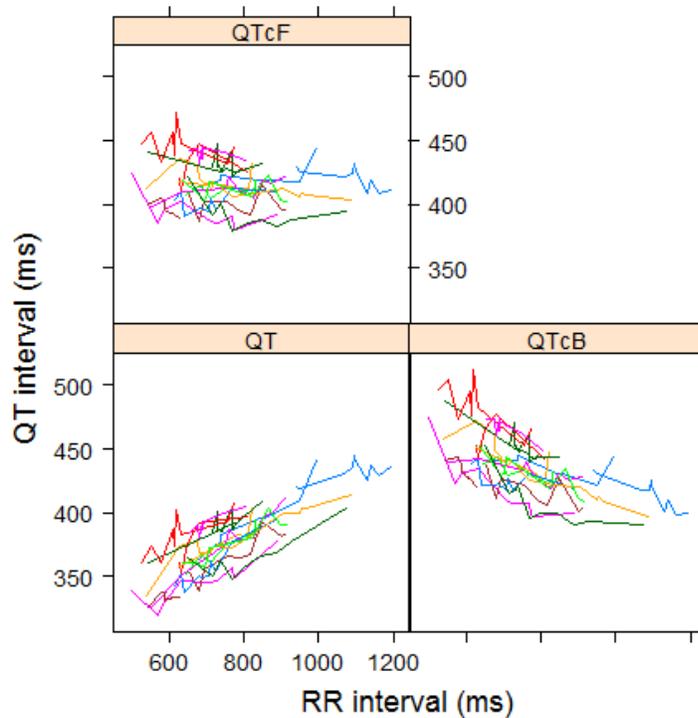
Reviewer's Analysis: An independent analysis was conducted by FDA reviewer and presented in Section 5.3. A delayed effect was observed with Lutathera on QTc prolongation; therefore, further exposure-response analyses for QTc were not conducted.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 3. QTcF was used for the primary statistical analysis.

**Figure 3: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Lutathera

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect. The model includes time as a fixed effect and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 5: Analysis Results of  $\Delta$ QTcF for Lutathera**

Time (Hour)	$\Delta$ QTcF (ms)			
	N	LSMean	SE	90% CI
Middle of Infusion	18	-4.1	1.4	(-6.5, -1.7)
End of Infusion (EOI)	18	-3.9	2.2	(-7.7, -0.1)
20min after EOI	15	-2.2	1.7	(-5.2, 0.8)
40min after EOI	16	-0.6	2.7	(-5.2, 4.0)
1 Hour after EOI	17	0.7	2.2	(-3.1, 4.5)
2 Hour after EOI	18	2.8	2.4	(-1.4, 7.0)
4 Hour after EOI	17	3.9	3.9	(-2.8, 10.6)
8 Hour after EOI	17	10.2	3.4	(4.3, 16.2)
24 Hour after EOI	16	11.3	3.2	(5.7, 16.9)

The largest upper bound of the 2-sided 90% CI for the mean change from baseline in QTcF ( $\Delta$ QTcF) was 16.9 ms at 24 hours post the end of infusion.

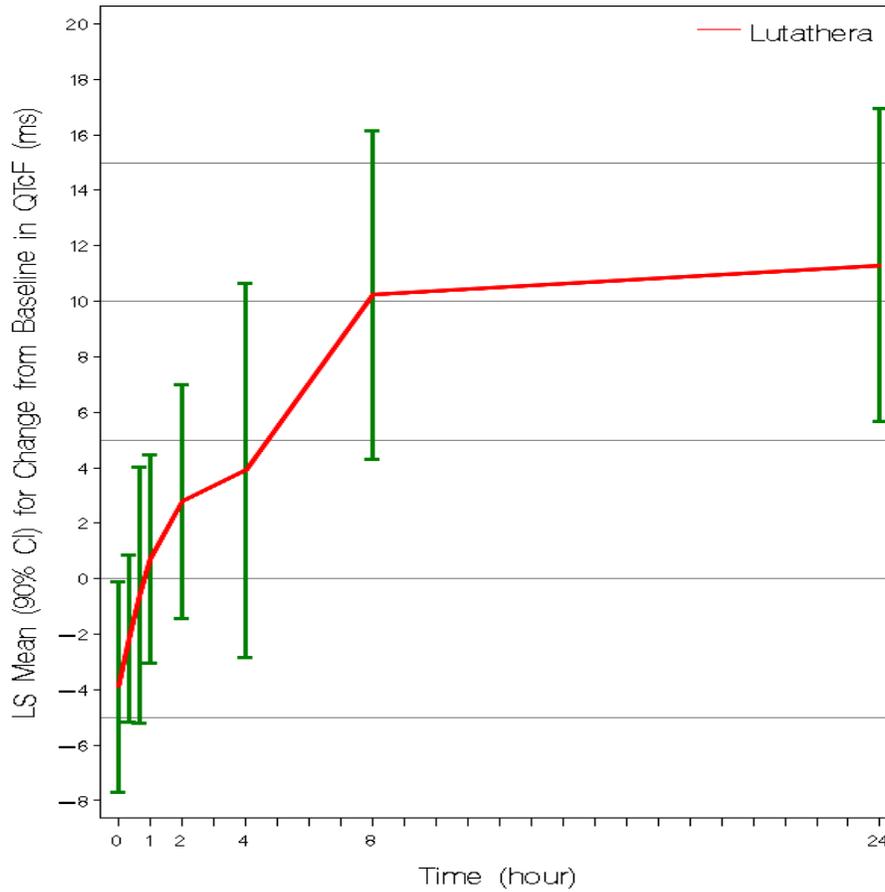
#### 5.2.1.2 Assay Sensitivity Analysis

Not Applicable.

#### 5.2.1.3 Graph of $\Delta$ QTcF Over Time

The following figure displays the time profile of  $\Delta$ QTcF for Lutathera.

**Figure 4: Mean and 90% CI  $\Delta$ QTcF Timecourse**



#### 5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values were  $\leq 450$  ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 6: Categorical Analysis for QTcF**

Treatment	Total N		QTcF $\leq 450$ ms		450 < QTcF $\leq 480$ ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	14	18	14 (100%)	18 (100%)	0 (0.0%)	0 (0.0%)
Lutathera	14	161	13 (92.9%)	157 (97.5%)	1 (7.1%)	4 (2.5%)

Table 7 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline in QTcF was above 60 ms.

**Table 7: Categorical Analysis of  $\Delta$ QTcF**

Treatment	Total N		$\Delta$ QTcF $\leq$ 30 ms		30 $<$ $\Delta$ QTcF $\leq$ 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Lutathera	14	152	11 (78.6%)	148 (97.4%)	3 (21.4%)	4 (2.6%)

**5.2.2 HR Analysis**

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 8. The largest HR increasing effect was observed at 8 hours post the end of infusion with mean  $\Delta$ HR value of 18.7 bpm (90% CI: 12.4 to 25.0 bpm).

**Table 8: Analysis Results of  $\Delta$ HR for Lutathera**

Time (Hour)	$\Delta$ HR (ms)			
	N	LSMean	SE	90% CI
Middle of Infusion	18	2.3	2.4	(-1.8, 6.5)
End of Infusion (EOI)	18	5.5	2.2	(1.6, 9.4)
20min after EOI	15	5.3	2.3	(1.4, 9.3)
40min after EOI	16	7.8	2.9	(2.8, 12.8)
1 Hour after EOI	17	7.4	2.6	(2.9, 11.8)
2 Hour after EOI	18	9.8	3.6	(3.5, 16.1)
4 Hour after EOI	17	13.1	3.1	(7.7, 18.6)
8 Hour after EOI	17	18.7	3.6	(12.4, 25.0)
24 Hour after EOI	16	3.0	4.1	(-4.1, 10.1)

The outlier analysis results for HR are presented in Table 9.

**Table 9: Categorical Analysis of HR**

Treatment	Total N	HR $\leq$ 100 bpm	HR $>$ 100 bpm	HR $>$ 45 bpm	HR $\leq$ 45 bpm
		Subj. #	Subj. #	Subj. #	Subj. #
Baseline	14	14 (100%)	0 (0.0%)	14 (100%)	0 (0.0%)
Lutathera	14	8 (57.1%)	6 (42.9%)	14 (100%)	0 (0.0%)

### 5.2.3 PR Analysis

Similar statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest mean change from baseline in PR ( $\Delta$ PR) was 5.0 ms with a 90% CI of 0.6 ms to 9.5 ms, which was observed at the end of infusion. PR changes were small and not statistically significant at other time points.

The outlier analysis results for PR are presented in Table 11.

**Table 10: Analysis Results of  $\Delta$ PR for Lutathera**

Time (Hour)	$\Delta$ PR (ms)			
	N	LSMean	SE	90% CI
Middle of Infusion	17	4.1	2.7	(-0.4, 8.6)
End of Infusion (EOI)	17	5.0	2.7	(0.6, 9.5)
20min after EOI	15	3.3	2.8	(-1.3, 7.9)
40min after EOI	16	3.7	2.7	(-0.9, 8.2)
1 Hour after EOI	17	-2.2	2.7	(-6.7, 2.3)
2 Hour after EOI	18	-0.1	2.7	(-4.5, 4.4)
4 Hour after EOI	17	-1.9	2.7	(-6.4, 2.5)
8 Hour after EOI	17	-4.1	2.7	(-8.6, 0.3)
24 Hour after EOI	14	2.3	2.8	(-2.5, 7.0)

**Table 11: Categorical Analysis for PR**

Treatment	Total N		PR $\leq$ 200 ms		PR $>$ 200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	14	18	12 (85.7%)	16 (88.9%)	2 (14.3%)	2 (11.1%)
Lutathera	14	157	12 (85.7%)	141 (89.8%)	2 (14.3%)	16 (10.2%)

### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The mean changes from baseline in QRS ( $\Delta$ QRS) were small and not clinically significant.

The outlier analysis results for QRS are presented in Table 13.

**Table 12: Analysis Results of  $\Delta$ QRS for Lutathera**

Time (Hour)	$\Delta$ QRS (ms)			
	N	LSMean	SE	90% CI
Middle of Infusion	18	-0.4	0.4	(-1.1, 0.2)
End of Infusion (EOI)	18	-0.5	0.3	(-1.0, -0.0)
20min after EOI	15	-0.6	0.2	(-1.0, -0.2)
40min after EOI	16	-0.8	0.3	(-1.3, -0.3)
1 Hour after EOI	17	-0.0	0.4	(-0.7, 0.7)
2 Hour after EOI	18	-1.1	0.3	(-1.7, -0.5)
4 Hour after EOI	17	-1.0	0.4	(-1.7, -0.4)
8 Hour after EOI	17	-0.9	0.6	(-1.9, 0.2)
24 Hour after EOI	16	0.3	0.8	(-1.2, 1.7)

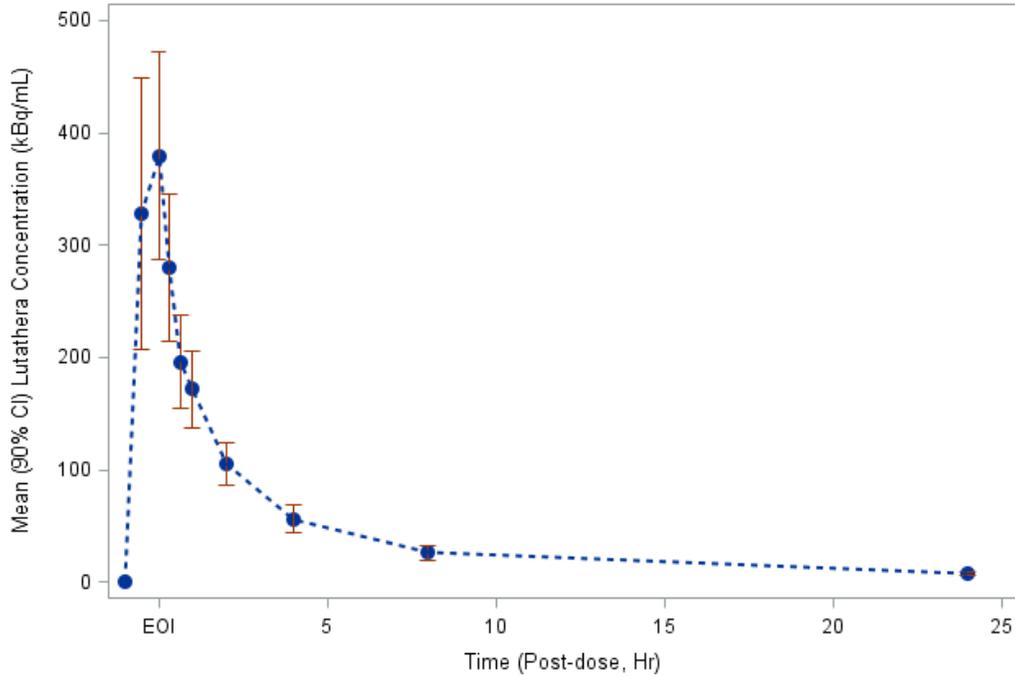
**Table 13: Categorical Analysis for QRS**

Treatment	Total N		QRS $\leq$ 110 ms		QRS $>$ 110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	14	18	12 (85.7%)	16 (88.9%)	2 (14.3%)	2 (11.1%)
Lutathera	14	161	9 (64.3%)	141 (87.6%)	5 (35.7%)	20 (12.4%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean temporal profile of drug concentration (in terms of decay adjusted radioactivity) is illustrated in Figure 5.

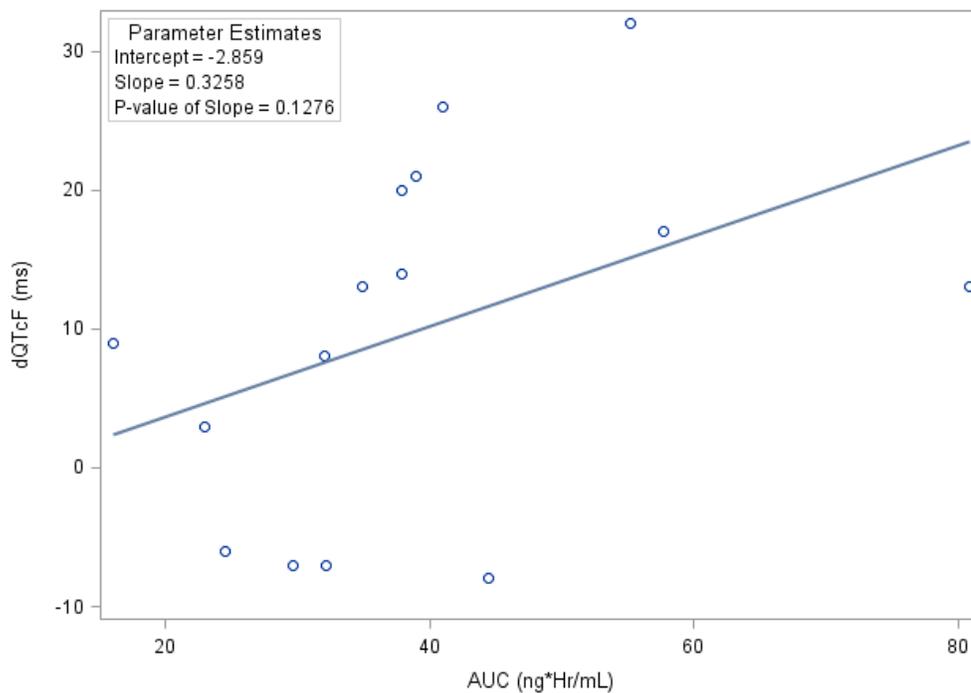
**Figure 5: Mean Lutathera concentration-time profile for IV treatment with 7.4 GBq of Lutathera ( $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ )**



EOI= End-of-infusion

The exploratory plots of the concentration-time course (Figure 5) and  $\Delta\text{QTcF}$ -time course (Figure 4) show that the maximum QTc change did not occur around  $T_{\text{max}}$  of drug concentrations but at a later time point (the last time point of 24 hour post dose evaluated in the study), suggesting substantial delayed effect with Lutathera treatment. Given the delayed effect and the study was not well controlled by the placebo and positive treatments, further concentration-QTc analyses was not conducted. Overall, there was only a single dose level that was studied in this trial and the relationship between  $\Delta\text{QTcF}$  at 24 hours and drug AUC (effect with cumulative exposure) was not statistically significant ( $p=0.128$ ) with the limited data in this study (Figure 6). Thus, conclusions regarding exposure-response relationship cannot be made.

**Figure 6:  $\Delta$ QTcF at 24 hours post dose vs. Lutathera AUC**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

Safety data was not provided in the cardiac safety report for the ECG sub-study.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	<p>Four intravenous treatments of 7.4 GBq of <math>^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> each, with an 8 week recommended interval between administrations.</p> <p>7.4 GBq of <math>^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> contain approximately 200 <math>\mu\text{g}</math> of <math>\text{DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> peptide.</p> <p>Exposure after a single administration of 7.4 GBq of <math>^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> is <math>41.36 \pm 14.95 \text{ ng}\cdot\text{h/mL}</math> (Mean AUC <math>\pm</math> SD) of total peptide – data from <a href="#">NETTER-1 PK analysis report</a>, Module 5.3.3.2.</p>
Maximum tolerated dose	<p>Single doses higher than 7.4 GBq of <math>^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> (containing about 200 <math>\mu\text{g}</math> of <math>\text{DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> peptide), administered for 4 times, with a cumulative radioactive dose of 29.6 GBq, were not tested in human. This dose has proven to be well tolerated in Phase I/II and in Phase III studies. In repeated dose toxicity studies in animals performed with the cold compound, the No-Observed Effect Level (NOEL) in rats was 1250 <math>\mu\text{g/kg}</math>, while the No-Observed Adverse Effect Level (NOAEL) in dogs was 3200 <math>\mu\text{g/kg}</math>.</p>

Principal adverse events	<p>In the Phase III NETTER-1 study the most frequent adverse events were nausea (59%), vomiting (47%), fatigue (40%), diarrhea (29%), musculoskeletal pain (29%), abdominal pain (26%), thrombocytopenia (25%), lymphopenia (18%), decreased appetite (18%).</p> <p>When looking at the laboratory data, it is to be noted that hematologic toxicities were underreported as adverse events by investigators. The frequency of leukopenia, thrombocytopenia, neutropenia, lymphopenia and anemia were multiplied by 11, 6, 5, 2 and 2 respectively in the Lutathera arm whereas they remained pretty stable in the controls. Most of them were of low severity and transient. Frequency of grade 3 or 4 hematologic toxicities in the Lutathera arm were not significantly increased vs. baseline patient status compared to control arm except for lymphopenia (multiplied by 22 in active arm but stable in control arm). The underreporting of severe lymphopenias as adverse events can be explained by the fact that it is well known that this lineage is highly impacted by Peptide Receptor Radionuclide Therapy but without any clinically relevant consequences (no difference in the reporting of infectious diseases was observed between the two arms). The causality of nausea / vomiting was confounded by the emetic effects of the concomitant amino acids infusion. Some other adverse events such as pain and fatigue were attributable to the underlying metastatic neuroendocrine tumor disease in many cases. As expected, besides nausea, vomiting and fatigue, hematologic toxicities were the most common adverse reactions possibly related to <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate administration according to investigators (thrombocytopenia 23%, lymphopenia 14%, anemia 12%, leukopenia 9%, neutropenia 5% and pancytopenia 1.8%).</p> <p>The pooled analysis of serious adverse events from the Integrated</p>
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	Summary of Safety (n = 921 patients treated with <sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate from the Erasmus MC Phase I/II and the NETTER-1 Phase III studies) also confirmed those findings.	
Maximum dose tested	Single Dose	7.4 GBq of <sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate containing approximately 200 µg of DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate peptide
	Multiple Dose	7.4 GBq of <sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate administered for 4 times with an 8 week recommended interval between administrations
Exposures Achieved at Maximum Tested Dose	Single Dose	As above, the exposure value calculated in the Dosimetry, Pharmacokinetic and ECG sub-study of the NETTER-1 Phase III study, for the total peptide content, is 41.36 ± 14.95 ng*h/mL (Mean AUC ± SD). In terms of radioactivity, the exposure achieved after administration of 7.4 GBq of <sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate is about 0.4 Gy, expressed as total body absorbed dose (the doses absorbed by normal organs/tumors are detailed in the <a href="#">NETTER-1 Dosimetry report</a> , Module 5.3.3.2)
	Multiple Dose	In terms of total peptide dose, the 4 treatments spaced by 8 weeks can be considered as a single dose administration, from a classical PK point of view). Regarding the radioactive dose, the cumulative effect of the 4 administrations must be considered. The estimated cumulative absorbed dose for the total body after 4 administrations of 7.4 GBq (29.6 GBq total) is 1.5 Gy ± 0.8 Gy (the doses absorbed by normal organs/tumors are detailed in the <a href="#">NETTER-1 Dosimetry report</a> , Module 5.3.3.2).
Range of linear PK	In animals, the exposure to the peptide was found to be dose-proportional over the whole dose range tested (1250 µg/kg to 20000 µg/kg in rats and 80 µg/kg to 3200 µg/kg in dogs).	
Accumulation at steady state	N.A. (4 intravenous treatments spaced by 8 week interval)	
Metabolites	In vitro metabolism data in human hepatocytes, in which no metabolic degradation of <sup>175</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate was observed, and RP-HPLC analysis of urine samples of the 20 patients included in the Dosimetry, pharmacokinetic and ECG sub-study, show that <sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate is poorly metabolized and is excreted mainly as intact compound by renal route.	
Absorption	Absolute/Relative Bioavailability	N.A. (intravenous administration)
	Tmax	N.A. (intravenous administration)
Distribution	Vd/F or Vd	Total peptide: Vz = 464 L ± 248 L (Mean ±

		SD). Considering the radioactive nature of the compound, the distribution was also evaluated by dosimetry analysis. The detailed description of the results is included in the <a href="#">NETTER-1 Dosimetry report</a> , Module 5.3.3.2.
	% unbound	Total peptide: 25.0% ± 3.0% (data from in vitro binding study at the expected plasma concentration in patients – see Report in Module <a href="#">4.2.2.3</a> )
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route = renal</li> <li>• % dose eliminated = about 60% of the administered dose eliminated by renal excretion within the first 16/23 hours, about 70% within 24/48 hours</li> </ul> <p>The remaining 30% is expected to be cleared by renal elimination in the days following Day 3 (as per dosimetry data)</p>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Total peptide: 71.7 h ± 28.1 h (Mean ± SD)</li> <li>• Mean ± SD for metabolites: N.A. (no evidence of metabolization)</li> </ul>
	CL/F or CL	Total peptide: 4.53 ± 1.42 L/h (Mean ± SD)
Intrinsic Factors	Age	Because of the radioactive nature of this drug product and because of its mechanism of action, it was considered more relevant to evaluate the effect of intrinsic factors on the organ absorbed doses (obtained from dosimetry evaluation) rather than considering a classical PK approach in this analysis. No correlations that could be relevant from a clinical point of view were found between selected intrinsic factors and absorbed doses in the potential critical organs, i.e. kidney and bone marrow.
	Sex	
	Race	
	Hepatic & Renal Impairment	No studies in hepatic and renal impaired patients performed (see Module 2.5, Section <a href="#">2.5.3.1.1</a> )
Extrinsic Factors	Drug interactions	No significant inhibitory or induction effects on human CYP450 enzymes and no specific interactions with P-gp indicate no potential for <sup>175</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate to cause clinically relevant drug-drug interactions. Therefore no specific clinical studies were performed.
	Food Effects	N.A.
Expected High Clinical Exposure Scenario	No increase in exposure above the range determined in the Dosimetry, Pharmacokinetic and ECG sub-study of the NETTER-1 Phase III study is expected, based on the following:	

	<ul style="list-style-type: none"> <li>- the dose in terms of radioactivity is precisely defined and measured before administration.</li> <li>- it is given intravenously, so absorption variability is not a factor that could have an impact on exposure</li> <li>- renal function must meet pre-defined criteria for the patient to be eligible for treatment with Lutathera, and therefore no relevant differences in renal elimination are expected</li> <li>- no evidence was found regarding compound metabolization. Therefore, no impact on compound fate due to possible metabolic differences is expected.</li> </ul>
Preclinical Cardiac Safety	<p>The possible effects of <math>^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> formulation on hERG tail current have been tested <b>in vitro in HEK-293 cells stably transfected with hERG-1 cDNA</b>. No relevant effects of the compound on the hERG tail current have been observed, indicating no particular potential for the compound to cause prolongation of the cardiac action potential or increase of QT interval. The absence of any effect on the cardiac conduction times was also confirmed in the <b>in vivo study in Beagle dogs</b>, in which the effects of <math>^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> on blood pressure, heart rate, body temperature and electrocardiogram (duration of PR, PQ, QT and QRS) after single i.v. administration were investigated. The results of this study showed that the compound does not have any effect on cardiac conduction times or body temperature, and does not cause arrhythmia at the doses tested (from 80 up to 800 <math>\mu\text{g}/\text{kg}</math>, that is 10 to 100 fold the intended human dose, scaled to dog based on body surface area), indicating that the compound does not have any effect on the cardiac conduction tissue. <math>^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}</math> showed to have a hypertensive effect associated with a reflex mediated bradycardia when administered intravenously, either as bolus (80, 250 and 800 <math>\mu\text{g}/\text{kg}</math>) or slow infusion (40 <math>\mu\text{g}/\text{kg}</math> and 80 <math>\mu\text{g}/\text{kg}</math>).</p>

Clinical Cardiac Safety	<p>In a substudy to the phase III trial NETTER-1, 20 subjects underwent serial PK and ECG assessment, and results were assessed using exposure response (ER) analysis. ECGs were measured at a central ECG laboratory (b) (4) at which the ER analysis was also performed. The ER analysis demonstrated a very shallow and statistically significant slope of the relationship between the <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate decay corrected activity concentrations and the effect on the QTc interval: -0.009 msec; 90% CI: -0.016 to -0.002. The predicted ΔQTcF effect using ER analysis was 0.98 msec (90% CI: -2.77 to 4.74) at the observed geometric mean peak decay corrected activity level (402 kBq/ml) after dosing with <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate, which is consistent with the small changes observed at individual timepoints, post-dosing. <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate did not have any effect on cardiac conduction (PR and QRS intervals).</p> <p>When assessing the NETTER-1 Phase III randomized controlled study adverse events alone, no cases of torsade de pointes, seizure or ventricular tachycardia, fibrillation or flutter were reported. Two cases of prolonged QT interval were reported in Lutathera arm (2%) vs. 1 in control arm (1%). One of those cases was reported as related to Lutathera according the investigator. In the Sponsor's view the main culprit in triggering the repeated acute episodes of QTc prolongation could be ondansetron medication, with a background contribution of an underlying predisposition (medical history of heart disease and chronic medication with anxiolytic: delorazepam).</p> <p>The incidence of syncope was also higher in Lutathera arm (5%, 3% when considering only the grade 3 or 4) than in the control arm (2%, 1%). The most relevant serious cases which could be linked with cardiac outward signs were:</p> <p>One 62-year old female patient who experienced a second degree atrioventricular block and syncope which led to pacemaker insertion due to risk of sudden cardiac death. According to the Investigator, a worsening of the underlying atrioventricular block had occurred after investigational treatment start. This event can also be related to known patient's risk factors (hypertension and type 2 diabetes mellitus), however, the relationship with Lutathera administration protocol cannot be totally excluded. A role of concomitant amino acid infusion seems more likely (through hyperkalemia commonly reported during amino acid infusion) than a role of Lutathera itself. However, blood potassium at time of events was not available, thus the available data do not allow validating this hypothesis.</p> <p>One 66-year old male patient who experienced a syncope episode followed by hospitalization because of disease aggravation and then sudden cardiac arrest leading to death. According to investigator the event was not related to study drug. The root etiology of the sudden chain of events was most probably the underlying malignancy (either tumor bleeding into the gastro-intestinal tract or tumor erosion into blood vessels) and its secondary and tertiary complications (state of shock that was multifactorial - hypovolemic / hemorrhagic, septic...), although comorbid events such as gastroesophageal reflux disease aspirations may have surely contributed.</p>
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	<p>Of note, in this study incidence of atrial fibrillation was higher in the Lutathera arm 4% (all of grades 1 or 2) than in the control arm (0%).</p> <p>From the pooled analysis of Integrated Summary of Safety (n = 921 patients treated with <sup>177</sup>Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate from the Erasmus MC Phase I/II and the NETTER-1 Phase III studies) the incidence of serious adverse events of interest for assessing drug proarrhythmic potential was limited. No cases of torsade de pointes, seizure or ventricular fibrillation or flutter were reported. Two cases (0.2% of patients) of sinus tachycardia and 1 case (0.1%) of tachycardia of unspecified origin were reported, but no cases of ventricular tachycardia were observed.</p> <p>Six cases (0.7%) of syncope were reported which however could not be formally attributed to cardiac events except for the patients from the NETTER-1 study mentioned above.</p>
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEVI KOZELI on behalf of HUIFANG CHEN

07/07/2016

Signing for Huifang because she is on leave.

QIANYU DANG

07/07/2016

DHANANJAY D MARATHE

07/07/2016

JIANG LIU

07/07/2016

MICHAEL Y LI

07/07/2016

CHRISTINE E GARNETT

07/07/2016

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # <b>208700</b>	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Lutathera Established/Proper Name: lutetium Lu 177 dotatate ( <sup>177</sup> Lu-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate) Dosage Form: Injection for intravenous infusion Strengths: 370 MBq/mL (b) (4)		
Applicant: Advanced Accelerator Applications USA, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: April 28, 2016 (3 <sup>rd</sup> part of rolling application) Date of Receipt: April 28, 2016 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: December 28, 2016	Action Goal Date (if different):	
Filing Date: June 27, 2016	Date of Filing Meeting: June 8, 2016	
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of patients with (b) (4) somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut [neuroendocrine tumors (b) (4)]		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<b><i>The application will be a priority review if:</i></b>	<input type="checkbox"/> Pediatric WR
<ul style="list-style-type: none"> <li><b><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></b></li> <li><b><i>The product is a Qualified Infectious Disease Product (QIDP)</i></b></li> <li><b><i>A Tropical Disease Priority Review Voucher was submitted</i></b></li> <li><b><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></b></li> </ul>	<input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <b><i>NO - N/A</i></b> <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track Designation –granted April 21, 2015 for IND 077219 <input type="checkbox"/> Breakthrough Therapy Designation ( <i>set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager</i> ) <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 077219

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <b><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i></b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If affected by AIP, has OC been notified of the submission?</b> <b>If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b>(NDAs/NDA Efficacy Supplements only)</b>				
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes</b> , answer the bulleted questions below:		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>		<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  <b>If yes</b> , # years requested:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes,</b> did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup> <b>If not,</b> explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CMC IR sent on May 18, 2016 requesting confirmation from the sponsor.
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sponsor submitted Form 3542a after FDA sent an IR on 5/17/16 requesting it.
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Clinical sent an IR as the applicant did not include financial disclosure forms signed by the applicant.

<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Sponsor submitted Form 3674 after they received the ACK LTR with the related request to submit it.
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b>PREA</b>				
Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan designation granted on January 12, 2009.
<b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BCPA:</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proprietary name conditionally acceptable May 27, 2016.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> <b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OPDP consult uploaded 5/2/16.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No MedGuide, PPI, IFU
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	IRT/QT uploaded 5/3/16; OSI uploaded 5/26/2016; Maternal uploaded 5/18/16; DMIP uploaded 6/1/16.
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> March 8, 2011 PIND/Pre-Phase 3 meeting  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-Phase 3 Minutes issued March 25, 2011.
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> March 14, 2016 Pre-NDA meeting  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-NDA Minutes issued March 17, 2016.
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <u>N/A</u>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** June 8, 2016

**BACKGROUND:** This NDA with orphan designation proposes the use of Lutathera for the treatment of patients with [REDACTED]<sup>(b) (4)</sup> somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut [neuroendocrine tumors [REDACTED]<sup>(b) (4)</sup>]. Fast Track designation under IND 077219 was granted on April 21, 2015. A PIND/Pre-Phase 3 meeting was held on March 8, 2011, and a pre-NDA meeting was held on March 14, 2016. AAA submitted a request for rolling submission under IND 077219 on March 17, 2016, with their plan for submitting portions of the proposed application, and FDA granted their request on March 22, 2016. A total of three submissions were received: complete modules 3 (quality) and 4 (nonclinical), and portions of module 2 on March 31, 2016; module 5 (clinical) on April 18, 2016; module 1 and remaining module 2 sections on April 28, 2016, the final official receipt date.

**Summary of Discussion:** The team confirmed that the application is fileable, with any filing issues identified to be conveyed in a day 60 letter (or day 74 letter if not possible by day 60). Information requests will be included in the day 60 letter or sent separately to the sponsor based on missing information and/or clarification requests.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Susan Truitt	Y
	CPMS/TL:	Melanie Pierce	Y
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Y
Division Director/Deputy	Patricia Keegan and Steven Lemery		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Joohee Sul	Y
	TL:	Suzanne Demko	Y
Clinical Pharmacology	Reviewer:	Brian Furmanski	Y
	TL:	Hong Zhao	Y
• Genomics	Reviewer:	Sarah Dorff	N

Biostatistics	Reviewer:	Lan Huang	Y
	TL:	Kun He	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Anwar Goheer	Y
	TL:	Whitney Helms	Y
Product Quality (CMC) Review Team:	ATL:	Eldon Leutzinger	Y
	RBPM:	Steven Kinsley	Y
• Drug Substance	Reviewer:	John Amartey	N
• Drug Product	Reviewer:	John Amartey	N
• Process	Reviewer:	John Amartey	N
• Microbiology	Reviewer:	Peggy Kriger	N
• Facility	Reviewer:	Krishnakali Ghosh	Y
• Biopharmaceutics	Reviewer:	Banu Zolnik	Y
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)		Danae Christodoulou and Anamitro Banerjee, CMC Branch Chiefs; John Arigo, Micro Branch Chief	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Carole Broadnax	Y
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Janine Stewart	Y
	TL:	Chi-Ming (Alice) Tu	N
OSE/DRISK (REMS)	Reviewer:	Mei-Yean Chen	Y
	TL:	Naomi Redd	N

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	N
Other reviewers/disciplines			
DPV	Reviewer:	Peter Waldron	Y
	TL:	Afrouz Nayernama	N
DEPI	Reviewer:	Carolyn McCloskey	N
	TL:	Steve Bird	N
Other Filing Meeting Attendees	Jennie Chang, Associate Director for Labeling		Y
	Latonia Ford, OSE RPM		Y
	Amy McKee, DOP2 Medical Officer		Y
	Lorraine Pelosof, DOP 2 Medical Officer		Y
	Christos Mastroyannis, DPMH Reviewer		Y
	Tamara Johnson, DPMH Team Leader		Y
	Denise Johnson-Lyles, DPMH RPM		Y
	Cynthia Welsh, DMIP Medical Officer		Y
	Devi Kozeli, IRT/QT RPM		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505 b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Clinical will send separate information requests to the sponsor about missing information.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: Clinical study design is acceptable.
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE

<b>Comments:</b>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>  <b>Comments:</b> Information requests will be sent to the sponsor.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>  <b>Comments:</b> Information requests will be sent to the sponsor.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b> CMC plans to send information requests to the sponsor.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/>
<b><u>New Molecular Entity (NDAs only)</u></b>  <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b><u>Environmental Assessment</u></b>  <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no,</b> was a complete EA submitted?</p> <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b> <u>N/A</u></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>What late submission components, if any, arrived after 30 days?</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO – Applicant did not submit Form 3474, Form 3542a (Patent), a complete list of CRO/CRO tasks, a clear list of sites, and the correct financial disclosure forms FDA 3454 and/or 3455, but provided these upon request via FDA IRs.</p>

<ul style="list-style-type: none"><li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li></ul>	<input checked="" type="checkbox"/> YES – after an IR was sent to request a clear list. <input type="checkbox"/> NO
<ul style="list-style-type: none"><li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li></ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Richard Pazdur	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): July 27, 2016	
<b>21<sup>st</sup> Century Review Milestones</b> (listing review milestones in this document is optional): Filing Meeting: June 8, 2016 Filing Action: June 27, 2016 Mid-Cycle Meeting: July 27, 2016 Wrap Up Meeting: November 18, 2016 <b>Comments:</b> Team confirmed during the Filing Meeting that an Advisory Committee meeting is not currently required.	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 60-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
<b>ACTION ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. N/A
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

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Annual review of template by OND ADRAAs completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUSAN B TRUITT  
06/22/2016

MONICA L HUGHES  
06/22/2016

# REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208700

**Application Type:** NME NDA

**Drug Name(s)/Dosage Form(s):** Lutathera ( $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate) injection, for intravenous use:  
370 MBq/mL (b) (4)

**Applicant:** Advanced Accelerator Applications USA, Inc.

**Receipt Date:** April 28, 2016

**Goal Date:** December 28, 2016

## 1. Regulatory History and Applicant's Main Proposals

This NDA with orphan designation, granted January 12, 2009, proposes the use of Lutathera for the treatment of patients with (b) (4) somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut [neuroendocrine tumors (b) (4)]. Fast Track designation under IND 077219 was granted on April 21, 2015. A PIND/Pre-Phase 3 meeting was held on March 8, 2011, and a pre-NDA meeting was held on March 14, 2016. AAA submitted a request for rolling submission under IND 077219 on March 17, 2016, with their plan for submitting portions of the proposed application, and FDA granted their request on March 22, 2016. A total of three submissions were received: complete modules 3 (quality) and 4 (nonclinical), and portions of module 2 on March 31, 2016; module 5 (clinical) on April 18, 2016; module 1 and remaining module 2 sections on April 28, 2016, the final official receipt date.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In summary, the following labeling issues were identified:

### Highlights of General Format

## RPM PLR Format Review of the Prescribing Information

1. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.

The current length of the HL is more than one-half page. If, during review and labeling discussions, the HL remains more than one-half page, the applicant could submit a request for a waiver of this requirement and will be advised of this in the day 60 filing letter.

2. A horizontal line must separate:
  - HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

A horizontal line does not separate the items above; the applicant will be asked to revise.

3. “Headings in HL must be presented in the following order:”

Recent Major Changes (RMC) does not need to be included as this is an original label. Applicant will be asked to remove this section instead of listing it with “Not applicable.”

4. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Bullet is not needed since there is only one dosage form. Applicant will be advised to remove the bullet.

5. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**”

A toll-free number is not listed for the U.S. manufacturer (current labeling lists (b) (4) ); the applicant will be asked to revise to include a toll-free number.

6. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

The subsections are not in title case; for example, should read “Patient Preparation,” etc. Applicant will be asked to revise.

### **Full Prescribing Information (FPI)**

7. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

## RPM PLR Format Review of the Prescribing Information

The subsections are not in title case; for example, should read “Patient Preparation,” etc. Applicant will be asked to revise.

8. When adverse reaction data are included from clinical trials (typically in the “Clinical Trials Experience” subsection), the following **verbatim** statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

The verbatim statement above does not precede the presentation of adverse reactions from clinical trials; the applicant will be asked to revise the labeling to include this statement.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the day 60 day filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format, both clean and red-lined track changes versions, by July 11, 2016. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

### Highlights

See Appendix for a sample tool illustrating Highlights format.

#### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.  
*Comment: No comments.*
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.  
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.  
*Comment: Length of HL is longer than one-half page and sponsor did not submit a waiver request. The applicant will be asked to revise.*
- NO** 3. A horizontal line must separate:  
• HL from the Table of Contents (TOC), **and**  
• TOC from the Full Prescribing Information (FPI).  
*Comment: No HL separates the TOC from the FPI.*
- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.  
*Comment: No comments.*
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.  
*Comment: No comments.*
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.  
*Comment: No comments.*
- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
---------	-------------------

## Selected Requirements of Prescribing Information

• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

***Comment:*** RMC does not need to be included as this is an original label. Applicant included this section with "Not applicable" indicated. Applicant will be asked to remove this section. All else is ok.

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.  
***Comment:*** No comments.

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.  
***Comment:*** No comments.

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.  
***Comment:*** No comments.

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.  
***Comment:*** No comments.

#### Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

## Selected Requirements of Prescribing Information

**Comment:** *No comments.*

- YES** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:** *No comments.*

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:** *No comments.*

- YES** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

**Comment:** *No comments.*

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:** *RMC does not need to be included as this is an original label. Applicant included this section with "Not applicable" indicated. Applicant will be asked to remove this section.*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

**Comment:** *See #16 Comment.*

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:** *See #16 Comment.*

### Dosage Forms and Strengths in Highlights

- NO** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:** *Bullet is not needed since there is only one dosage form. Applicant will be advised to remove the bullet.*

### Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

## Selected Requirements of Prescribing Information

**Comment:** *No comments.*

### Adverse Reactions in Highlights

- NO** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

**Comment:** *A toll-free number is not provided (current labeling lists (b) (4)); the applicant will be asked to revise to include a toll-free number.*

### Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Comment:** *No comments.*

### Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

**Comment:** *No comments.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.  
*Comment:* No comments.
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:* No comments.
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:* No comments.
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:* No comments.
- NO** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:* The subsections are not in title case; for example, should read “Patient Preparation,” etc. Applicant will be asked to revise.
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:* No comments.
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:* No comments.

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

**NO**

31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:** The subsections are not in title case; for example, should read "Patient Preparation," etc. Applicant will be asked to revise.*

**YES**

## Selected Requirements of Prescribing Information

32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

***Comment:*** No comments.

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

***Comment:*** No comments.

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

***Comment:*** No comments.

#### BOXED WARNING Section in the FPI

- YES** 35. All text in the BW should be **bolded**.

***Comment:*** No comments.

- YES** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

***Comment:*** No comments.

#### CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

***Comment:*** This section does list contraindications.

#### ADVERSE REACTIONS Section in the FPI

- NO** 38. When adverse reaction data are included from clinical trials (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

***Comment:*** The verbatim statement above does not precede the presentation of adverse reactions from clinical trials; the applicant will be asked to revise the labeling to include this statement.

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

## Selected Requirements of Prescribing Information

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:** *No comments.*

### PATIENT COUNSELING INFORMATION Section in the FPI

**N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:** *No comments.*

**N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:** *No comments.*

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

**PROPRIETARY NAME** is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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SUSAN B TRUITT  
06/22/2016