APPLICATION NUMBER:

208700Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th><strong>Application Type</strong></th>
<th>NDA</th>
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<td><strong>Application Number</strong></td>
<td>208700</td>
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<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>January 26, 2018</td>
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<td><strong>OSE RCM #</strong></td>
<td>2017-1540, 2017-1542</td>
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<tr>
<td><strong>Reviewer Name(s)</strong></td>
<td>Mei-Yean Chen, Pharm.D.</td>
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<tr>
<td><strong>Team Leader</strong></td>
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<td><strong>Division Director</strong></td>
<td>Cynthia LaCivita, Pharm.D.</td>
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<td><strong>Review Completion Date</strong></td>
<td>December 8, 2017</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>¹⁷⁷ Lu-DOTA²-Tyr³-Octreotate</td>
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<tr>
<td><strong>Trade Name</strong></td>
<td>Lutathera</td>
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<tr>
<td><strong>Name of Applicant</strong></td>
<td>Advanced Accelerator Applications USA, Inc. (AAA)</td>
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<td><strong>Therapeutic Class</strong></td>
<td>peptide receptor radionuclide</td>
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<td><strong>Formulation(s)</strong></td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>7.4 GBq (200 mCi) intravenously for 4 doses</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Lutathera (177 Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate) is necessary to ensure the benefits outweigh its risks. Advanced Accelerator Applications USA, Inc. (AAA) submitted a New Drug Application (NDA) 208700 for Lutathera with the proposed indication for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors in adults.

DRISK and the Division of Oncology Products 2 (DOP 2) agree that a REMS is not needed to ensure the benefits of Lutathera outweigh its risks. The main serious adverse events are due to radiation exposure. The critical organs for radiation toxicity with Lutathera are kidney and bone marrow. To mitigate the risk of kidney toxicity, the proposed label contains recommendations for administering an amino acid solution containing L-lysine and L-arginine as an intravenous infusion 30 minutes before, during, and for at least 3 hours following Lutathera infusion. Myelosuppression, secondary myelodysplastic syndrome and leukemia, renal toxicity, hepatotoxicity, neuroendocrine hormonal crises, embryo-fetal toxicity, and male infertility will be conveyed in Warnings and Precautions. The labeling review is still ongoing at this time. If approved, the radiation risks will be included in Warnings and Precautions to communicate minimizing the risks of radiation exposure consistent with institutional good radiation safety practices.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lutathera (177 Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate) is necessary to ensure the benefits outweigh its risks. AAA submitted a New Drug Application (NDA) 208700 for Lutathera with the proposed indication for the treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults. This application is under review in the Division of Oncology Product 2 (DOP2). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Lutathera (177 Lu-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate), an NME, is a radiolabeled somastatin analog proposed for the treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults. The drug substance lutetium (Lu 177) oxodotreotide is a radionuclide chelated to a cyclic peptide by the means of a covalently bound chelator. Lutetium decays to stable hafnium (Hf 177) with a half-life of 6.7 days by emitting beta radiation.

Lutathera binds to somatostatin receptors with highest affinity for somatostatin subtype 2 receptors (SSRT2). Lutathera is administered as intravenous infusion. Once in the blood stream, the molecule

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.
binds to the somatostatin receptor expressing cells, including malignant SSRT2-positive tumors, and the compound is internalized. The beta emission from Lu 177 induces cellular damage by formation of free radicals in SSRT2-positive cells in neighboring cells. Lutathera is proposed as a solution of 7.4 GBq (200 mCi) to be given intravenously every 8 week for a total of 4 doses. b Lutathera was approved by the European Medicines Agency in September 2017.

2.2 Regulatory History
The following is a summary of the regulatory history for Lutathera relevant to this review:

- January 12, 2009: Orphan drug designation granted.
- March 31, 2016: Sponsor submitted Lutathera NDA 208700.
- August 11, 2016: The Sponsor committed to provide the FDA with clean datasets and reviewers guide during the mid-cycle meeting.
- December 19, 2016: FDA issued a Complete Response (CR) letter due to the sponsor deficiencies in meeting FDA requirements for electronic datasets.
- September 29, 2017: The European Commission (EC) approved Lutathera
- October 30, 2017: Midcycle meeting – No major safety concerns identified at this time that would require a REMS.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition
Neuroendocrine cells are distributed widely throughout the body, and neoplasms of these cells, which are termed neuroendocrine tumors (NETs) can arise at many sites. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are NETs arising usually within the digestive system. Well-differentiated carcinoid tumors over-express somatostatin subtype 2 receptors (SSRT2) which is a common feature of all GEP-NETs.  

A long-standing classification system divides gastrointestinal (GI) neuroendocrine tumors into foregut, midgut and hindgut tumors. The classification is based on the embryonic origin of the different tumors. The foregut primaries, which account for up to 25% of cases, arise in the lung, thymus, stomach, or proximal duodenum. Midgut tumors, which account for up to 50% of cases, arise in the small intestine, appendix, or proximal colon. Hindgut tumors, which account for approximately 15% of cases, arise in the distal colon or rectum. Note that some of these locations (lung and thymus) are outside the definition of GEP-NETs, so the classification system has contributed to some confusion. A more recent World Health Organization (WHO) classification system has been developed which is considered more clinically relevant. The current WHO classification specifies 4 subtypes under 2 main categories and is relevant for all neuroendocrine tumor types:

b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
• Neuroendocrine neoplasm (well differentiated): grade 1 and grade 2
• Neuroendocrine carcinoma (poorly differentiated):
  1. Grade 3, small cell carcinoma
  2. Grade 3, large neuroendocrine carcinoma

GEP-NETs may also be divided into functioning and non-functioning tumors. Functioning tumors clinically present with symptoms related to overproduction of biogenic amines and peptide hormones. The majority of GEP-NETs does not secrete sufficient levels of biologically active substance to induce symptoms and are therefore classified as non-functioning and often present fairly late with symptoms of mass effect, or distant metastases. Delayed diagnosis is typical (5-7 years) in patients with non-functioning GEP-NETs, resulting in greater morbidity, increased probability of metastatic disease, and increased mortality. At the time of diagnosis, a significant percentage of patients have hepatic metastasis.

The classical symptoms of carcinoid syndrome include flushing (80%), diarrhea (70%), abdominal pain (40%), valvular heart disease (30-40%), telangiectasia (25), wheezing (15%), and pellagra-like skin lesions (5%). Carcinoid heart disease is characterized by plaque-like fibrous endocardial thickening that classically involves the right side of the heart, occurring in 50-70% of patients with a carcinoid syndrome. The disease is most likely induced by chronic tumor secretion of serotonin, which binds to cardiac 5-HCT receptors. Hemodynamically significant heart disease is seen in about 5-10% of patients.

Among patients with low or intermediate-grade histology and distant disease, survival is highly variable. In patients with advanced carcinoid tumors, outcomes are worse for patients with lung and colon primary tumors (median survival 17 and 7 months, respectively) and most favorable for tumors arising in the jejunum, ileum, and cecum (median survival 55 to 65 months).

The prevalence of neuroendocrine tumors in the United States during 2004 is estimated to be 3.4 per 100,000 persons and with a living population of 103,312. Adjusting for an annual 4% increase in incidence, the living population in the US for 2015 is estimated to be about 159,000.

### 3.2 Description of Current Treatment Options

The clinical management involves a multi-modal approach including surgery, cytoreductive treatment, embolization, chemo-embolisation, radiotherapy, chemotherapy, and somatostain analogues. The FDA approved pharmacotherapy is shown in the table below.

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\(^c\) Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

\(^d\) Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*
### Table: Summary of Treatment Options Relevant to Proposed Indication.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Year of Approval</th>
<th>Indication</th>
<th>Dosing</th>
<th>Important Safety and Tolerability Issues</th>
<th>Risk Management Approaches</th>
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<tr>
<td><strong>FDA Approved Treatments</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide (Sandostatin LAR), 1998&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td>Symptomatic tx of meta. Carcinoid tumors</td>
<td>20 mg intramuscular injection every 4 weeks</td>
<td>Gallbladder abnormalities, hypo or hyperglycemia, hypothyroidism, bradycardia, arrhythmia.</td>
<td>Warnings &amp; Precautions</td>
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<tr>
<td>Everolimus (Afinitor), indication pancreatic NET approved 2011, for GI or lung NET approved 2016&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td>Prog., well-diff., non-functional NET of GI or lung origin that are unresectable, locally adv. or meta. disease</td>
<td>10 mg oral once daily</td>
<td>Non-infectious pneumonic infections, angioedema, stomatitis, renal failure, impaired wound healing, embryo-fetal toxicity</td>
<td>Warnings &amp; Precautions</td>
</tr>
<tr>
<td>Sunitinib (Sutent), approved 2011 for pancreatic NET&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>Prog., well-diff. pancreatic NET that are unresectable, locally adv. Or meta. disease</td>
<td>37.5 mg oral once daily</td>
<td>Hepatotoxicity (boxed warning), cardiovascular events, QT prolongation, hemorrhagic events, tumor lysis syndrome, hypertension</td>
<td>Boxed warning; Warnings &amp; Precautions</td>
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<tr>
<td>Lanreotide (Somatuline Depot) 2014&lt;sup&gt;8&lt;/sup&gt;</td>
<td></td>
<td>unresectable, well or moderately-diff., locally advanced or meta. GEP-NETs</td>
<td>120 mg intramuscular injection every 4 weeks</td>
<td>Gallstones may occur, hypo and/or hyperglycemia, and decrease heart rate</td>
<td>Warnings &amp; Precautions</td>
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### 4 Benefit Assessment

NETTER-1, a multicenter, open label, and randomized phase 3 study, compared treatment with Lutathera (116 patients) with treatment with octreotide LAR (113 patients) in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors. Patients were randomized to receive Lutathera (7.4 GBq every 8-16 weeks for up to 4 administrations) with octreotide long-acting...
release (LAR) (30 mg by intramuscular injection every 4 weeks) or octreotide LAR 60 mg (by intramuscular injection every 4 weeks) alone (control arm). Randomization was stratified by OctreoScan tumor uptake score and the length of time that patients had been on the most recent constant dose of octreotide.

The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee (IRC). The additional efficacy outcome measures were objective response rate (ORR) and overall survival (OS). Disease progression was reported in 13% of patients in the Lutathera arm versus 54% of patients in the control arm. The median PFS for the Lutathera arm was not reached at the time of analysis whereas in the control arm, PFS was 8.5 month with P-value less than 0.0001. The ORR was 13% in the Lutathera arm versus 4% in the control arm with P-value of 0.0148. The OS in the Lutathera arm was not reached whereas in the control arm it was 27.4 months.

The efficacy of Lutathera in patients with GEP-NETs was assessed in the ERASMUS study, a single institution, open-label, single-arm trial which enrolled 1,214 patients with somatostain receptor positive tumors. Most patients were Dutch (811 patients) with the remaining (403 patients) were residents of various European and non-European countires. The main analysis was conducted on 811 Dutch patients with different somatostatin receptor positive tumor types. The mean age was 60 years and 56% of patients had progressed within 12 months of treatment and 10% had received prior chemotherapy. Lutathera 7.4 GBq was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. Fifty-two percent of patients received Lutathera with octreotide LAR. The major efficacy outcome was investigator assessed ORR by SouthWest Oncology Group (SWOG) crieteria, which was later converted to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1). Of 360 patients with GEP-NETs, the ORR rate was 45% and Complete Response (CR) was 3%.

5 Risk Assessment

The safety data are based on pooled data from NETTER-1 and ERASMUS studies. In the NETTER-1 trial, Lutathera was administered with an amino acid solution and octreotide LAR in 111 patients with advanced, progressive midgut neuroendocrine tumors. Safety data was obtained in an additional 833 patients (22 patients in non-randomized pharmacokinetic sub-study from NETTER-1 and 811 patients with advanced somatostain receptor positive tumors, including midgut neuroendocrine tuors from ERASMUS). The main analysis was conducted on 811 Dutch patients with different somatostatin receptor positive tumor types.

In the NETTER-1 trial, deaths were reported in 5% of patients in the Lutathera arm compared to 8% in the control arm.

^ Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
The critical organs for radiation toxicity with Lutathera are kidney and bone marrow, which may occur many months or years following the treatment. Monitoring the kidney and bone marrow function are required and adapt the treatment protocol if necessary (dose, infusion interval, and number of infusions) before each administration and during the treatment.

If approved, labeling will include the following risks in the Warnings and Precautions section, as well as recommended dose modifications to manage toxicities in labeling section 2.3 and 2.4:

- **Myelosuppression:** In NETTER-1, myelosuppression occurred more frequently in patients receiving Lutathera with octreotide LAR compared to patients receiving octreotide LAR alone – (all grades and grade 3 or 4): anemia: 81% and 0%; thrombocytopenia: 53% and 1%; neutropenia: 26% and 3%.

- **Secondary Myelodysplastic Syndrome and Leukemia:** In NETTER-1 study, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving Lutathera with octreotide LAR compared no patients receiving octreotide LAR alone. In ERASMUS study, the median time to the development was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

- **Renal toxicity:** In the ERASMUS study, less than 1% of patients developed renal failure 3 to 36 months following Lutathera. Two of these patients had underlying renal impairment or risks factors for renal failure (diabetes or hypertension) and required dialysis. The proposed label includes recommendations for the administration of amino acid solution before, during, and after Lutathera to decrease the reabsorption of Lutathera through the proximal tubules to decrease the radiation dose to the kidneys.

- **Risk of hepatic toxicity:** In the ERASMUS study, severe abdominal and epigastric pain were reported in less than 1% of patients; it developed hours to days following Lutathera administration. Two patients (<1%) were reported to have tumor hemorrhage, edema or necrosis with one patient experiencing intrahepatic congestion and cholestasis. Radiation exposure to the liver may be increased in patients with hepatic tumors.

- **Neuroendocrine hormonal crises:** manifesting with flushing, diarrhea, bronchospasm, and hypotension, occurred in 1% of patients in the ERASMUS study and typically occurred during or within 24 hours following the initial Lutathera dose. Two (<1%) patients were reported to have hypercalcemia.

- **Embryo-fetal toxicity:** all radiopharmaceuticals, including Lutathera, have the potential to cause fetal harm.

- **Risks of male infertility:** in a subset of 35 men from ERASMUS, decreased inhibin-B and increased FSH were observed 3 months following Lutathera. The recommended cumulative dose of 29.6 GBq of Lutathera results in a radiation absorbed dose to the testis within the range where temporary or permanent infertility can be expected following external beam radiotherapy. Consider cryopreservation of sperm in male patients.
Expected Postmarket Use

Lutathera therapy is limited to inpatient settings, and is prepared and administered by nuclear medicine physicians and staff with appropriate radiation training. Like other radionuclide drugs, Lutathera will not be marketed to the general population.

Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Lutathera beyond routine pharmacovigilance and labeling. The applicant did propose .

Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks of Lutathera, DRI SK considers patient population size, seriousness of disease, expected benefit of the drug, the expected duration of treatment, and the seriousness of known or potential adverse reactions.

The prevalence rate of neuroendocrine tumors in the United States during 2004 is estimated to be 3.4 per 100,000 persons and with a living population of 103,312. Adjusting for an annual 4% increase in incidence, the living population in the US for 2015 is estimated to be about 159,000.

GEP-NETs patients with early stage disease are often asymptomatic or present with poorly defined symptoms. At the time of confirmed diagnosis, a significant percentage of GEP-NET patients have hepatic metastasis. Delayed diagnosis is typical (5-7 years) in patients with non-functioning GEP-NETs, resulting in greater morbidity, increased probability of metastatic disease, and increased mortality.

In the case of inoperable disease, neither chemotherapy nor external beam radiation therapy are considered effective. There are few treatment options with significant efficacy for patients with advanced disease. Most of the products approved in the targeted indication have limited application because they are only approved for use in sub-populations of GEP-NET patients. There is a clear unmet need for an effective therapeutic option in this population.

Based on the efficacy and safety information currently available, the clinical reviewers recommend approval of Lutathera. The NETTER-1 study and ERASMUS study both demonstrated the efficacy of Lutathera. The main serious risks are due to radiation exposure. The critical organs for radiation toxicity with Lutathera are kidney and bone marrow. Section 2.3 “Premedication and concomitant medications” in the proposed label provides detailed instructions to give amino acid solution before, during, and after Lutathera to decrease the reabsorption of Lutathera through the promimal tubules to decrease the radiation dose to the kidneys; section 2.4 “Dose Modifications” of the proposed label communicates how to decrease/withhold/discontinue Lutathera for myelosuppression. The risks of renal toxicity, myelosuppression, secondary MDS, neuroendocrine crises, embryo-fetal toxicity, and risk of male infertility will be described in the Warnings and Precautions section of the label. The labeling review is still ongoing at this time. If approved, the risks of radiation exposure will in .

Warnings and Precautions to communicate minimizing the risks of radiation exposure consistent with
institutional good radiation safety practices. In addition, radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore a REMS is not necessary for Lutathera to ensure its benefits outweigh its risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

1. Klimstra DS, Yang z, Pathology, classification, and grading of neuroendocrine tumors arising in the digestive system, UpToDate, accessed October 16, 2017


3. Chan JA, Kulke M, Metastatic well-differentiated gastrointestinal neuroendocrine (carcinoid) tumors: System therapy options to control tumor growth and symptoms of hormone hypersecretion, UpToDate, accessed October 16, 2017


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/s/

MEI-YEAN T CHEN
12/08/2017

CYNTHIA L LACIVITA
12/10/2017
Concur
Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review

Date: November 21, 2016
Reviewer(s): Mei-Yean Chen, Pharm.D.
Division of Risk Management (DRISK)
Team Leader: Naomi Redd, Pharm.D., DRISK
Division Director: Cynthia Lacivita, Pharm.D., DRISK

Drug Name(s): Lutathera (¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate)
Therapeutic Class: Radioisotope Agent
Dosage and Route: 7.4 GBq (200 mCi) intravenously for 4 doses
Application Type/Number: NDA 208700
Applicant/sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
OSE RCM #: 2016-809
This document is to defer Division of Risk Management (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Lutathera (Lutathera (\textsuperscript{177}Lu-DOTA\textsuperscript{0} -Tyr\textsuperscript{3}-Octreotate), NDA 208700.

A 505(b)(1) application for Lutathera was received by the Division of Oncology Products 2 (DOP2) from Advanced Accelerator Applications USA, Inc. (AAA) on April 28, 2016, with the proposed indication for the treatment of patients with [redacted] somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors or carcinoid tumors.

During a teleconference October 21, 2016 with AAA, DOP2 communicated that due to AAA’s deficiencies in meeting FDA requirements for electronic datasets, DOP2 plans to issue a Complete Response (CR) letter. DOP2 also communicated that AAA could choose to withdraw their application, request a Type A meeting for follow up and clarification regarding requirements for a new application submission.

An evaluation of the need for REMS for Lutathera will be undertaken by DRISK after AAA resubmits the NDA for review. Please send DRISK a new consult request at such time. This memo serves to close the existing consult request to DRISK for Lutathera under NDA 208700.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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MEI-YEAN T CHEN
11/20/2016

CYNTHIA L LACIVITA
11/20/2016
Concur