CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208700Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	208700
PDUFA Goal Date	January 26, 2018
OSE RCM #	2017-1540, 2017-1542
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 8, 2017
Subject	Evaluation of Need for a REMS
Established Name	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
Trade Name	Lutathera
Name of Applicant	Advanced Accelerator Applications USA, Inc. (AAA)
Therapeutic Class	peptide receptor radionuclide
Formulation(s)	
Dosing Regimen	7.4 GBq (200 mCi) intravenously for 4 doses

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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^{0}-Tyr^{3}-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 contain L-lysine and L-arginine as an intravenous infusion 30 mintues before, during, and for at least 3 hours following Lutathera infusion. Myelosuppression, secondary myelodysplastic syndrome and leukemia, renal toxicity, heptaic toxicity, 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 in a (b) (4) 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^{0}-Tyr^{3}-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^{0}-Tyr^{3}-Octreotate), an NME,[a] 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 emiting beta radiation.

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

[a] 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 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.
- July 26, 2017: The Sponsor resubmitted Lutathera NDA 208700.
- 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.[1]

A long-standing classification system divides gastrointestinal (GI) neuroendocrine tumors into foregut, midgut and hindgut tumors.[2] The classification is based on the embryoinic 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) classficiation system has been developed which is considered more clinically relevant.[3] The current WHO calssfication specifes 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.*

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