

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208547Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management Review

Application Type	NDA
Application Number	208547
Submission #	S00-1
OSE RCM #	2015-2166
Reviewer Name(s)	Naomi Redd, Pharm.D., Acting Team Leader
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 4, 2015
Subject	Evaluation to determine if a REMS is necessary
Established Name	^{68}Ga -DOTA ⁰ -Tyr ³ Octreotate/gallium-68 (^{68}Ga) DOTATATE
(Proposed) Trade Name	(b) (4) ®
Applicant	Advanced Accelerator Applications (AAA) USA Inc.
Therapeutic Class	Diagnostic Radiopharmaceutical
Formulation(s)	Single-use kit containing one vial of lyophilizate containing 40mcg of DOTATATE, one vial of 1 mL of reaction buffer solution, and one accessory cartridge
Dosing Regimen	2 MBq/kg (0.054 mCi/kg) administered as an IV bolus injection
Proposed Indication(s)	(b) (4) use with positron emission tomography (PET) imaging in the detection of somatostatin receptor (b) (4) neuroendocrine tumors (b) (4) NETs)

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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 (NME) ⁶⁸GaDOTATATE (b) (4) is necessary to ensure the benefits of this product outweigh its risks. The applicant, AAA USA, Inc. submitted a New Drug Application (NDA) 208547 for ⁶⁸GaDOTATATE with the proposed indication for (b) (4). The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Medical Imaging Products (DMIP) agree that a REMS is not needed to ensure the benefits of ⁶⁸GaDOTATATE outweigh its risks.

1 Introduction

This review by DRISK evaluates whether a risk evaluation and mitigation strategy (REMS) for the NME ⁶⁸GaDOTATATE (b) (4) is necessary to ensure the benefits of this product outweigh its risks. The applicant, AAA USA, Inc. submitted NDA 208547 for ⁶⁸GaDOTATATE with the proposed indication for (b) (4). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

⁶⁸Ga-DOTATATE is a diagnostic radiopharmaceutical, and is not used to treat any disease or medical condition. This product is a conjugated somatostatin analogue that binds to somatostatin receptors (SSTR) in cancerous tissues.¹ These receptors are over-expressed in (b) (4) NETs, and to a varying extent in other tissue carcinomas that may be found in the kidney, lung, prostate, and breast. The applicant's proposed indication is for (b) (4). FDA has modified the indication for (b) (4) use with PET imaging in the (b) (4) of SSTR bearing (b) (4) NETs.² The sensitivity of ⁶⁸Ga-DOTATATE imaging can vary among tumor types depending on the density and

¹ AAA USA, Inc Nonclinical Overview, Module 2.4 pg 1

² ⁶⁸Ga-DOTATATE draft labeling, December 1, 2015

amount of SSTRs that are present.³ Most of the literature for using ⁶⁸Ga-DOTATATE appears to be in the detection of (b) (4) NETs due to the high expression of SSTRs found in these malignancies.⁴

The recommended radioactivity to be administered is a single IV bolus injection of 2 MBq/kg of body weight (0.054 mCi/kg). It is supplied as a single dose kit containing: one vial of lyophilizate 40 micrograms of ⁶⁸GaDOTATATE, one vial of 1 milliliter of reaction buffer solution, and one accessory cartridge. This is a NME 505(b)(2) application, with Orphan Drug status, under Priority review with a PDUFA date of March 1, 2016. The efficacy of this product is based on available literature, results of a prospective comparative study conducted at the Vanderbilt University Medical Center (VUMC), and data from expanded access programs. ⁶⁸Ga-DOTATATE is not licensed in the United States; however, it is available in Europe, and in other countries such as Asia, Australia, and Latin America.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- 4/5/2011: IND 111972 opened for expanded access study at VUMC
- 5/14/2014: IND 122818 opened for literature review of ⁶⁸Ga-DOTATATE
- 7/1/2014: DMIP agreed to a literature based NDA supported by the results of the expanded access data conducted at VUMC
- 11/9/2014: DMIP provided advice on the methodology of the systematic review, toxicity scale, endpoints, and statistical analysis plan.
- 7/1/2015: FDA receives NDA 208547 for ⁶⁸GA-DOTATATE
- 10/13/2015: Midcycle meeting
- 10/27/2015: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data a REMS is not needed for ⁶⁸GA-DOTATATE, reference DAARTS 11/24/2015

³ AAA Inc USA Module 2.5 Clinical Overview, pg 5

⁴ Midcycle Meeting Clinical Slides, October 13, 2015

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Neuroendocrine tumors are a rare group of neoplasms that arise from the neural crest, and can be found in various tissues.⁵ These tumors may also arise from endocrine cell clusters in the thyroid, pancreas, adrenal medulla and pituitary glands. Neuroendocrine cell tumors have an incidence of approximately 35 cases per 100,000 people in the United States.⁶ A major characteristic of NETs is overexpression of somatostatin receptors in cancerous cells. These tumors can present diagnostic challenges due to varying degrees of their presentation in the body, which requires the need to use several techniques for diagnosis. Some of these procedures may include a combination of histopathology, conventional imaging, and evaluation of circulating biomarkers.⁷ This can make detection of these tumors difficult, which may delay management of the disease.⁵ Over 60% of patients with NETs do not get a proper diagnosis until the disease has metastasized. Distance location and grade of the lesions are important prognostic factors for managing these malignancies. The Surveillance Epidemiology and End Results (SEER) database analyses show median survival rates of 33 months in patients with Grade 1 or 2 distant metastatic disease; however, in patients with poorly differentiated tumors, median survival rates are only five months upon diagnosis.⁷

3.2 DESCRIPTION OF CURRENT DIAGNOSTIC OPTIONS

OctreoScan® (111In-octreotide) was the first somatostatin analogue approved by the FDA in 1985 for detection of NETs. Radiolabelled meta-iodobenzylguanidine (AndriView®) approved in 2008, and C-11 choline approved 2012, are other diagnostic radiopharmaceuticals used to detect SSTR containing tumors of other origins. As a class, diagnostic radiopharmaceuticals do not have a Boxed Warning in their respective labels, or have required a REMS for approval.

The table below summarizes these diagnostic modalities.

⁵ Punit S, et al. PET/CT imaging of neuroendocrine tumors with ⁶⁸Gallium-labeled somatostatin analogues: An overview and single institutional experience from India. *Indian J Nucl Med.* 2014 Jan-Mar; 29(1): 2 -12

⁶ Mojtahedi A et al. The value of ⁶⁸Ga-DOTATATEPET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging* 2014;4(5):426-434

⁷ Oberg K. Diagnostic work-up of gastroenteropancreatic neuroendocrine tumors. *Clinics (Sao Paulo).* 2012 Apr; 67(Suppl 1): 109-112

Table 1: Summary of Diagnostic Radiopharmaceutical Options Relevant to Proposed Indication

Product Trade Name (Generic)	Year of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
Indium IN 111 Pentetretotide (OctreoScan®) ⁸	1985	for scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors	111 MBq (3.0 mCi) IV for planar imaging; 222MBq (6.0 mCi) IV for SPECT imaging.	None known; <1% of 538 patients experienced dizziness, fever, flush, headache, hypotension, changes in liver enzymes, joint pain, nausea, sweating, and weakness.	None
Iobenguane I123 (AdreView®) ⁹	2008	for gamma-scintigraphy for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic test.	370 MBq (10 mCi) IV	<1% dizziness, rash, pruritis, flushing and injection site hemorrhage.	None
Choline C 11 ¹⁰	2012	diagnostic agent for PET imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging.	370 to 740 MBq (10 to 20 mCi) as a bolus IV injection	Mild injection site reactions (no numbers).	None

⁸ Octreoscan Prescribing Information, Radiopharmaceutical Internal Dosimetry Information Center, Oak Ridge Associated Universities, Oak Ridge, TN, February 1985; Revised October 2015

⁹ AdreView Prescribing Information, GE Healthcare, September 2008

¹⁰ Choline C11, Mayo Clinic PET Radiochemistry Facility, Rochester, MN, September 2012

Of these agents listed in Table 1, OctreoScan is the most similar to ^{68}Ga -DOTATATE, since its indication is for the localization and detection of neuroendocrine tumors that bear somatostatin receptors. Limiting factors with the use of OctreoScan include decreased efficiency of the test, prolonged imaging times, a higher radiation dose to patients, and low image quality. When ^{68}Ga -DOTATATE is added to PET scanning, lesion detectability is enhanced due to improved resolution of the images. In a review article written by Mojtahdei and colleagues, a figure of a side by side comparison of the detectability of NETs in ^{68}Ga -DOTATATE to OctreoScan is shown below⁶:

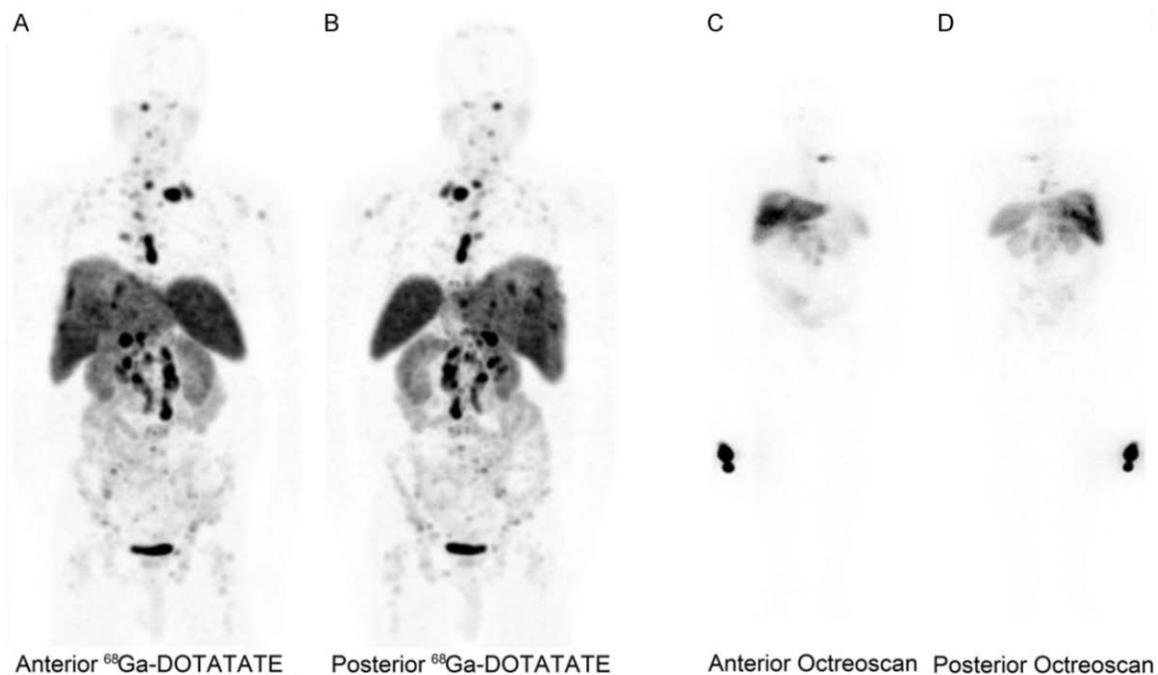


Figure 1. Side by side comparison of ^{68}Ga -DOTATATE to OctreoScan from one of our patients with neuroendocrine tumor. Anterior (A) and posterior (B) ^{68}Ga -DOTATATE pet images demonstrate extensive metastatic disease. OctreoScan anterior (C) and posterior (D) images from same patient demonstrate much fewer lesions indicating superior quality of PET/CT imaging.

4 Benefit Assessment

The evidence of clinical benefit is based upon a literature review and retrospective adaptation of an expanded access program. The clinical benefit of the product appears to be found in terms of increased sensitivity of the product over the currently approved product OctreoScan. The expanded access program assessed the images in a blinded fashion and found similar results with increased sensitivity.⁴

In a phase 1/2, open-label, single-center study comparing a single intravenous bolus injection of 200 MBq (5 mCi) of ^{68}Ga -DOTATATE to previously obtained standard of care imaging (CT, MRI, and/or octreotide scans) in adult patients with known or suspected neuroendocrine tumors, ^{68}Ga -DOTATATE results were consistent with the final diagnosis in 74 of 78 evaluable participants (95%).² When compared to the imaging performance of OctreoScan, the sensitivity for ^{68}Ga -DOTATATE was found to

be statistically significantly superior (96% [95% CI: 86, 100] vs. 72% [58, 84]; McNemar's χ^2 , $p = 0.003$).² This difference was mainly explained by the lower number of false negative for ⁶⁸Ga-DOTATATE (2 cases) compared to OctreoScan® (14 cases).² In regards to the impact on patient care management, adding ⁶⁸Ga-DOTATATE to the current imaging standard of care had a beneficial impact on 37% (29/78) of the patients. ⁶⁸Ga-DOTATATE identified 12 patients as non-surgical candidates. In contrast, 3 of these 12 (25%) patients were misclassified by OctreoScan®.² ⁶⁸Ga-DOTATATE exposes the patient to much less radiation due to the lower dose range, has enhanced image resolution when used with PET, and the scans can be completed in 2 hours versus in 2 days with OctreoScan.⁴ As per the FDA clinical reviewer for this product, the imaging community and the patient advocate groups are very vocal about the use ⁶⁸Ga-DOTATATE. Patients are willing to travel to a facility that offers the scan as well as pay up to \$5,000 for a scan. Because of these reasons, it is difficult to recruit for and conduct clinical trials. Furthermore, because of the manufacturing challenges that can occur with short half-life radionuclides, there are limited manufacturers who want to develop the product.

5 Risk Assessment & Safe Use Conditions

There are very limited adverse events documented in the literature with the use of ⁶⁸GaDOTATATE. In a study involving 97 patients, the following adverse reactions were possibly related to ⁶⁸GaDOTATATE: mild tachycardia in 1 patient, increased alanine aminotransferase in 1 patient, and hyperglycemia in 2 patients.² The Warnings and Precautions section of the label contain similar language that are found in all radiopharmaceuticals with limiting the exposure of radiation to the patient as much as possible, and ensuring appropriate handling of radioactivity. OctreoScan has a similar safety profile, with the frequency of adverse events being found in less than one percent of 538 patients observed in clinical trials as noted in Table 1. These adverse events were transient and included: dizziness, fever, flush, headache, hypotension, changes in liver enzymes, joint pain, nausea, sweating, and weaknesses. There was also one reported case of bradycardia and one case of decreased hematocrit and hemoglobin. None of these adverse events reported with ⁶⁸GaDOTATATE or in the OctreoScan label rose to grade level reporting. OctreoScan does not contain any Boxed Warnings, Contraindications, or Warnings and Precautions in its label. Similarly, the label for ⁶⁸GaDOTATATE does not contain any Boxed Warnings or Contraindications. The Warnings and Precautions section is under review at the time of this writing to include information on the risk for image misinterpretation.² This product is available as a single-use kit to be given as one dose, has a short half-life of 68 minutes, and imaging is conducted within 2 hours of the given dose. These factors limit patient exposure to any potential risk(s).

6 Expected Postmarket Use

Diagnostic radiopharmaceuticals are limited to inpatient settings, and are prepared and administered by nuclear medicine physicians and staff with appropriate radiation training. Like other imaging drugs, ⁶⁸GaDOTATATE will not be marketed to the general population which presents limited potential for off label use.

7 Discussion of Need for a REMS

Detection of neuroendocrine tumors can present with varying challenges due to several techniques that must be employed to identify these rare and heterogeneous malignancies. Over 60% of patients can present with metastatic disease upon initial diagnosis, and median survival rates can be as low as 5 months in patients with poorly identified tumors. Therefore, there is a need for agents that provide targeted identification and better imaging results in this patient population. ^{68}Ga -DOTATATE is a conjugated somatostatin analogue that binds to somatostatin receptors (SSTR), which are found in neuroendocrine tumors, with a high abundance found in (b) (4) NETs. The indication is for (b) (4) use with PET imaging in the detection of SSTR bearing (b) (4) NETs. OctreoScan is a similar FDA approved product for the scintigraphic localization of primary and metastatic NETs that bear SSTRs. Both of these products have similar mechanisms of action, are given as a single IV dose for diagnostic use, and have low incidences of adverse effects. None of the adverse effects that have been reported for both products required grading for seriousness or severity of an event, and neither of the product labels have Boxed Warnings. ^{68}Ga -DOTATATE will include language in the Warning and Precautions regarding the evaluation of interpreting images in the detection of NETs. However, ^{68}Ga -DOTATATE was shown to have better sensitivity and specificity for detecting NETs, and has better imaging results compared to OctreoScan. Furthermore, the radionuclide dose is smaller with ^{68}Ga -DOTATATE, and due to its shorter half-life, results can be obtained in approximately 2 hours versus in 2 days with OctreoScan. These features improve patient related outcomes by providing better diagnostic results in a shorter time frame, with less exposure to radiation. This in turn allows for quicker detection and management of disease.

As with other diagnostic radiopharmaceuticals, ^{68}Ga -DOTATATE will be restricted to inpatient settings. This product is expected to be used in combination with PET imaging for the detection of a rare and specific type of tumor, prepared and given by nuclear medicine physicians and staff who are required to have specialized training for the handling and management of radionuclides as part of their daily clinical practice. Past regulatory actions have not required a REMS for approval of these types of products.

8 Conclusion & Recommendations

In conclusion, DMIP and DRISK agree that risk mitigation measures beyond professional labeling are not warranted for ^{68}Ga -DOTATATE. Healthcare providers who use radiopharmaceuticals for the detection of tumors are familiar with the risks associated with these products and understand the importance of patient monitoring. Should DMIP have any concerns or questions, or if new safety information becomes available that changes the risk: benefit profile of this product, please send a consult to DRISK.

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