CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	June 1, 2016
From	Charles J. Ganley, M.D.
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	208547
Applicant Name	Advanced Accelerator Applications (AAA)
Date of Submission	7/1/2015
PDUFA Goal Date	6/1//2016
Proprietary Name / Established (USAN) Name	Netspot / Kit for the preparation of Ga 68 dotatate (^{68}Ga-DOTA^{0}-Tyr^{3}-octreotate) injection ;the source of Ga 68 is not included)
Dosage Forms / Strength	2 MBq/kg (0.54 mCi/kg) up to 200 MBq intravenously Mass dose is 40 mcg.
Applicant Proposed Indication(s)/Populations	(b) (4)
Action:	Approval
Approved Indication(s)/Populations (if applicable)	NETSPOT, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer Review	Cindy Welsh, M.D.
Statistical Review	Satish Misra, Ph.D., Jyoti Zalkikar, Ph.D. Thomas Gwise, Ph.D.
Pharmacology Toxicology Review	Ronald Honchel, Ph.D.
OPQ Review: Drug substance Drug Product, Environmental Assessment Process Facility Biopharmaceutics Microbiology Technical Lead	 Martin Haber Ph.D. John Amartey Ph.D. Dhanalakshmi Kasi Ph.D. Krishna Gosh Ph.D. Vidula Kohatkar Helen Ngai Ph.D. Eldon Leutzinger Ph.D.
Clinical Pharmacology Review	Christy John, Ph.D.
OPDP	Adam George, Pharm.D
OSI	John Lee, M.D.
CDTL Review	Alex Gorovets, M.D.
Project Manager	Modupe Fagbami
OSE/DMEPA	Michelle Rutledge, Pharm.D
OSE/DRISK	Cynthia LaCivita, Pharm.D., Naomi Redd, Pharm.D
Labeling Review	Michele Fedowitz, M.D., Nushin Todd, M.D., Ph.D.

OND=Office of New Drugs; OPQ=Office of Pharmaceutical Quality; OPDP=Office of Prescription Drug Promotion;
OSI=Office of Scientific Investigations; CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology; DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis; DRISK=Division of Risk Management

Section 1: Benefit-Risk Framework (BRF)

Benefit-Risk Summary and Assessment

Ga 68 dotatate is a drug that consists of a somatostatin analog peptide (Tyr^3-octreotate; 8 amino acids), a chelator (DOTA[1]) and Ga 68. After intravenous administration, Ga 68 dotatate will bind to somatostatin receptors (SSR), preferentially to SSR2 receptors, which can be found in normal tissue and in many neuroendocrine tumors (NETs). PET scans obtained after injection will show binding in the liver, spleen, pituitary and other organs that normally contain SSR. The binding of sites outside of the normal expected distribution can be utilized to identify the location of NETs. In some cases, if the SSR2 receptor density in NETs within normal tissue with SSR, the NETs can be detected. Not all NETs possess SSR2 in sufficient density to be identified on PET scanning, especially poorly differentiated tumors, but these poorly differentiated tumors may possess other SSR. Five different SSR (SSR1, SSR2, SSR3, SSR4, and SSR5) have been identified and other analogs currently under drug development may bind preferentially to some of these other SSR.

The clinical data provided included patients with a known diagnosis of NETs generally by biopsy with histologic confirmation and in some cases with blood or urine tests for chemicals that are known to be secreted by the NETs. Performance characteristics, specifically sensitivity and specificity, are not measureable with the data provided.

The application included a wide variety of issues that are addressed in this memo.

- Netspot is a kit comprised of a buffer solution, a lyophilized powder of dotatate and an accessory cartridge. The source of Ga 68 is not provided with the kit. It would be unrealistic to require that the kit and generator be purchased together because a single generator can produce many doses of Ga 68 and the generator (b) (4).
- The Eckert Ziegler GalliPharma Germanium Ge 68/Gallium Ga 68 generator (EZG) DMF was reviewed to support the application. As such, the safety and efficacy of the **Ga 68 dotatate** refers to the kit with Ga 68 generated by the EZG. AAA cannot promote the use of the kit with other Ge68/Ga68 generators that have not been reviewed as a part of this application. Use of the kit with alternative gallium generators can be supplemented to the application.
- The clinical data supporting the application was obtained from a Vanderbilt University Medical Center (VUMC) expanded access IND protocol. Because it was not originally intended to support a drug development application, (b) (4). Additional supportive clinical data was provided by a review of the medical literature.
- The dotatate provided in the kit, had not been administered to humans at the time of submission of the application. VUMC uses a different Eckert Ziegler 68Ge/68Ga generator in the production of Ga 68 dotatate There are quality control measures in place that allow the chemistry reviewers to believe that the dotatate will adequately bind with Ga 68.
- The application supports a localization indication in patients already diagnosed with a neuroendocrine tumor. It serves as an adjunct to other testing used for the detection of NET.
- Orphan drug status was granted for a management indication (b) (4). According to the Office of Orphan Drugs, the localization indication would fit within the broad designation of management.

The CTDL and Division Director believe that Netspot can be approved for a localization indication (structural indication) (b) (4). I agree with their assessments. (b) (4).

[1] 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid

Benefit Risk Table

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Somatostatin receptors** • SSR1, SSR2, SSR3, SSR4, and SSR5 have been characterized in the body • Present in normal tissue (spleen, liver, adrenals, kidneys, pituitary, salivary glands, thyroid) • SSR overexpress in NETs; expressed in different densities in NETs • SSR2 and SSR5 are expressed in 70% - 90% of NETs **Neuroendocrine Tumors (NETs)** • Relatively rare neoplasm with a prevalence of 2 – 6/100,000. • Heterogeneous group of neoplasms arising from endocrine cells in the pancreas, lung, GI tract • Metastasis in 60% at time of initial diagnosis. • The World Health Organization (WHO) classification scheme puts neuroendocrine tumors into three categories: (1) well-differentiated neuroendocrine tumors, further subdivided into tumors with benign and those with uncertain behaviors, (2) well-differentiated (low grade) neuroendocrine carcinomas with low-grade malignant behavior, (3) poorly differentiated (high grade) neuroendocrine carcinomas, which are the large cell neuroendocrine and small cell carcinomas[2] • SSR expression decreases as the histologic tumor grade increases; high grade tumors have limited SSR expression	The localization of the extent of NETs by multiple diagnostic tests is important for the characterization of this disease. PET/CT with Ga 68 dotatate offers a sensitive method to detect tumors that express SSR2. It can be utilized as an adjunct to conventional planar imaging with CT scan and MRI.
Current Diagnostic Options	• Computed tomography • Magnetic Resonance Imaging • In 111 pentetreotide (OctreoScan) SPECT/CT • ^{18}F FDG PET/CT	• Ga 68 dotatate will provide another diagnostic option in localizing NETs that express SSR2. It offers several advantages over In 111 pentetreotide:

[2] High Grade Neuroendocrine Tumours: NET Patient Foundation booklet dated February 2012

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Blood Tests biomarker (e.g. chromogranin A) • Urine Tests biomarker (e.g. 5-HIAA) • Molecular testing (e.g. Ki-67 Index)	1) only requires 4 hours for injection and test completion compared with >24 hours for In 111 pentetreotide; 2) less radiation exposure; 3) better resolution leading to better visualization of lesions; 4) gallium 68 generator is kept on site whereas In 111 is produced by a cyclotron offsite; and 5) possibly improve lesion detection. Limitation: will not detect NETs that do not express SSR2. • Other radioimaging tests (^{18}F FDG) may provide information if Ga 68 dotatate does not detect lesions. • Diagnostic performance characteristics and the value pf radiopharmaceuticals in patient management need to be established.
Benefit	**VUMC study** • included 98 patients of whom 78 had both Ga 68 dotatate and In 111 pentetreotide (usually done first and lag of up to 3 years difference between timing of tests) • 74 of 78 Ga 68 dotatate scans agree with conventional imaging (CT or MRI) **Literature studies** J Nucl Med 2010: 51:875-882. • Retrospective study • 51 patients with histologically proven NET • 120 – 200 MBq Ga 68 Dotatate administered; In 111 DTPA Octreotide • 2 readers by consensus, comparison to CT and/or MRI • 47/51 patients had disease on cross sectional imaging; 226 lesions identified	• From the information provided it is difficult to calculate the performance characteristics (sensitivity, specificity) of Ga 68 dotatate. • There is sufficient information to establish that Ga 68 dotatate binds to SSR2 and when doses of 2 MBq/kg are administered, NETs are detectable. • There are limitations in that some NETs may not express SSR2 in a sufficient density for detection but other imaging tests can be considered to address this deficiency. This test can be viewed as adjunct to other imaging tests to support the localization of NETs. • It offers advantages over In 111 pentetreotide with regard to resolution and convenience for the patient because it can be completed over several hours versus over a day or two for In 111 pentetreotide. • (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Ga 68 Dotatate detected disease in 41/47 patients; detected 168/226 lesions • Detection noted in the uncinate pancreas is a false positive. • In 5 patients with negative scan, 27 metastatic lesions were detected on CT +/- MRI. • There is no data in the article regarding the specifics for patient management. <u>J Med Imaging Radiat Oncol 2012:56:40-47.</u> • Retrospective study • 59 patients; 41 with proven NETs, 11 suspected METs, 4 paraganglioma/pheochromocytoma, 2 osteomalacia tumors • 76 Ga 68 Dotatate PET/CT scans;165 – 243 MBq administered • in 40/59 patients Ga 68 Dotatate PET/CT provided additional information compared with conventional imaging (CT, MRI, X-ray, bone scintigraphy) • in 33/40 this related to identification of disease in an additional organs or distant nodes; bone and distant nodes are most common • The article lacks detailed information to allow for a specific assessment of patient management. <u>Additional studies are included in reviews by the medical officer, CDTL and statistical reviewers that are not included here.</u>	(b) (4) There was inconsistency between the 2 literature reports in that one suggested that there was greater detection of lesions with CT and MRI whereas the other suggested the opposite; Ga 68 dotatate detected more lesions.
Risk	• Ga 68 has a half-life of 68 minutes • The radiation exposure is 3.15 mSv (compared to 26 mSv for In 111); the radiation exposure including the CT scan will be approximately 25 mSv. • The dose of DOTATATE is less than 50 mcg. • The PET images can be incorrectly read.	• The radiation exposure related only to Ga 68 is about 50% greater than the radiation exposure of a head CT scan. • The associated CT scan of the body contributes a radiation dose of approximately 20 mSv. • No pharmacologic effect is expected from the octreotate. • The risk of the test is minimal considering the seriousness

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The eluate from the generator is sterile. • Germanium breakthrough from the generator could occur and be administered to the patient. Germanium 68 has a half-life of 271 days. • Treatment of NETs with long acting or short acting somatostatin analogs could interfere with the binding of octreotate to the SSR2. • False positive findings occur in the uncinate process of the pancreas.	of the condition being evaluated. • If the images are read incorrectly, either over reading or under reading could lead to increased risks for the patient that could include inappropriate treatment for the extent of disease. The extent of disease should be confirmed by histopathology. • The application included a review of the Drug Master File for the EZG. The amount of germanium breakthrough has been evaluated for the EZG was found to be satisfactory to the chemists. The eluate passes through an accessory cartridge to capture Ge 68 break-through. • For patients being treated with somatostatin analog, the PET/CT scan should not be conducted within the timeframe outlined in the labeling. • The labeling identifies that the uncinate process positive finding is a normal variant.
Risk Management	• There is no significant risks for adverse events other than those associated with the test itself (sterility and Germanium break-through from generator) • Under and over reading of the scan.	• FDA has reviewed the DMF for the EZG generator and sterility is satisfactory. • The eluate passes through an accessory cartridge to capture Ge 68 break-through. • NETs are assessed with multiple modalities to accurately detect evidence of metastatic disease. Ga 68 dotatate adds an additional test to assist in the localization of disease. Histopathological confirmation of areas of uptake may be necessary.

Section 2. Further discussion to support regulatory action

Product Quality

- The kit includes vial #1 which is the reaction vial containing 40 mcg of dotatate and excipients as a lyophilized powder, vial #2 contains a buffer solution and an accessory cartridge is used to capture germanium-68 breakthrough (b) (4).
- The excipients in vial #1 (b) (4).
- The gallium-68 source is a gallium generator (a column with adsorbed germanium-68), a self-contained system that is on site. It is not provided with the kit. HCl is poured into the generator and the sterile eluate containing $^{68}GaCl3$ passes through the accessory cartridge. The eluate is collected in vial #1 and $^{68}GaCl_3$ reacts with dotatate to form. The contents of vial #2 are added immediately to vial #1 (b) (4).
- Gentisic acid is an excipient in vial #1 and (b) (4) (b) (4)
- DMF (b) (4) Eckert Ziegler generator $^{68}Ge/^{68}Ga$) was reviewed to provide a source of gallium-68.
- The clinical experience from VUMC was used to justify reliance on the literature. The comparability of the proposed product is bridged to the literature by demonstrating the same substance, Ga 68 dotatate is formed by comparison to the cold Ga-Dotatate reference standard.
- The strength of the proposed product is in the same range as the strengths of the drug products in the literature.
- Verification that Ga 68 dotatate is formed is performed by QC testing in the nuclear pharmacy.
- The quality of the dotatate is supported by information in the application.
- The labeling of the product reflects use of the kit with the Eckert Ziegler generator. If the sponsor would like to promote the use of the kit with other gallium generators, they should supplement the application with data to support the product quality.
- Refer to Dr. Leutzinger's summary review for additional details.

Nonclinical Pharmacology/Toxicology

The non-clinical safety data supporting the gallium 68 dotatate was extrapolated from testing of 177Lu-DOTATATE. There are no significant safety concerns. DOTATATE has a high affinity for SSR2 with the IC50 of .98 nM.

Clinical Pharmacology

- No dose finding studies were submitted and none were located in the literature.
- There are no pharmacokinetic studies. Biodistribution based on PET imaging of various organs was provided at 1, 2 and 3 hours after injection.
- The dose of 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 MBq) is recommended in dosing and is similar to the dosing in the VUMC study.
- There is no pharmacologic effect from the drug.
- Long and short acting somatostatin analogs competitively bind to somatostatin receptors in the body. Based on information from the current pattern of use in the literature, dosing of Ga 68 dotatate should be given (b) (4) long acting analog and 24 hours after a short acting analog. In patients being treated with long acting somatostatin analogs, the labeling states that imaging should occur just prior to dosing with long-acting somatostatin analogs.

Clinical/Statistical – Efficacy

The clinical data to support the effectiveness of Ga 68 dotatate included data from the VUMC expanded access protocol and from a review of the medical literature. A meta-analysis conducted by the sponsor and submitted was determined by the statistical reviewer to not be helpful for regulatory decision making. There was not sufficient information provided to allow for the calculation of sensitivity and specificity. The review of individual studies had limitations that included retrospective evaluations, poorly defined standard of truths, assessment based on reporting patients as positive or negative rather than presenting the assessment of individual lesions within a patient and in studies attempting to compare Ga 68 dotatate to In 111 pentetreotide scans, significant difference in the timing of the imaging tests (in some cases the difference may be as great as three years).

There was however, sufficient data to document that Ga 68 dotatate was able to detect NETs compared with conventional imaging (i.e. computed tomography or MRI) and in some cases confirmed by histology. (b) (4)

Safety

The VUMC Study inspection concluded that the protocol was not followed for the collection of safety data. This in part was an outgrowth of the study being conducted under an expanded access IND protocol. It was determined that this lack of safety information was not essential to approval because the mass dose of the drug is less than 50 mcg and radiation exposure to the gallium 68 is not excessive. In additional, there is safety data from the publications in the literature supporting the safety of the final drug product.

Advisory Committee Meeting

The application was not reviewed before an advisory committee.

Pediatrics

NETs are rare in children. There were no pediatric studies submitted with the application nor were children included in the VUMC data. The medical officer conducted a literature search and found three articles where Ga 68 dotatate was administered to pediatric patients. One of the articles provided information on pediatric patients with neuroblastomas and NETs. The dose used in the study was equivalent to the dose proposed for adults in this application. In 27 of 30 patients, Ga 68 dotatate was able to localize disease. Ga 68 dotatate is recommended to be dosed the same in children as in adults, on a weight basis.

Other Relevant Regulatory Issues

The diagnostic utility of the kit depends on the binding to gallium 68 to form the drug product Ga 68 dotatate. There was some discussion of weather this required that the approval of the kit also required the approval of the Ga 68 generator as a drug. It was determined that the kit could be approved with the DMF for the EZG being part of the approved application. Because of this, any changes to the EZG requires an update to the DMF by Eckert Ziegler. The applicant would also be required to provide information to the application.

The safety and effectiveness of the drug was supported by the review of the EZG DMF. The labeling reflects this review and the approval is based on use of the EZG with the kit. The sponsor can supplement the application with supporting information for other generators (i.e. right of reference to other generators) to support use of other generators with their kit.

Labeling

There are no outstanding labeling issues. Netspot is the kit which includes the ligand that is radiolabeled with Ga 68 for the production of the final drug product.

Orphan Drug Status

AAA received orphan designation for Ga 68 dotatate as a diagnostic tool for the clinical management of NETs. 21 CFR 315.4 outlines the different indications for diagnostic radiopharmaceuticals.

> Sec. 315.4 Indications
>
> (a) For diagnostic radiopharmaceuticals, the categories of proposed indications for use include, but are not limited to, the following:
>
> (1) Structure delineation;
>
> (2) Functional, physiological, or biochemical assessment;
>
> (3) Disease or pathology detection or assessment; and
>
> (4) Diagnostic or therapeutic patient management.
>
> (b) Where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical, or pathological process or to more than one disease or condition.

The application is being approved for a structural delineation indication per 21 CFR 315.4(a)(1) (b) (4) This issue was communicated with the Office of Orphan Drug Products. They noted that they view the structural indication to fall under the clinical management orphan designation; orphan exclusivity would be based on the specific approved indication.

Because there is the opportunity to improve on the diagnostic indication, the sponsor of this application or another sponsor could provide data to support an indication for therapeutic patient management which would improve on the structural delineation indication.

As noted in 316.31(b), the structural delineation indication would not prevent others from seeking other diagnostic indications for this drug and disease. NME exclusivity of 5 years, if granted, would delay another sponsor from obtaining an additional indication for this drug product.

> 21 CFR 316.31(b).
>
> Orphan-drug exclusive approval protects only the approved indication or use of a designated drug. If such approval is limited to only particular indication(s) or uses(s) within the rare disease or condition for which the drug was designated, FDA may later approve the drug for additional indication(s) or uses(s) within the rare disease or condition not protected by the exclusive approval. If the sponsor who obtains approval for these new indication(s) or uses(s) has orphan-drug designation for the drug for the rare disease or condition, FDA will recognize a new orphan-drug exclusive approval for these new (not previously approved) indication(s) or use(s) from the date of approval of the drug for such new indication(s) or use(s).

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/s/

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