

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208547Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 6, 2016
From	Alex Gorovets MD
Subject	Cross-Discipline Team Leader Review
NDA #	208547
Applicant	Advanced Accelerator Applications (AAA)
Date of Submission	July 1, 2015
PDUFA Goal Date	March 1, 2016 extended to June 1, 2016
Proprietary Name / Non-Proprietary Name	Netspot / gallium Ga 68 dotatate injection
Dosage form(s) / Strength(s)	2 MBq/kg up to 200MBq intravenously (IV)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	<i>Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	Ga 68 dotatate is indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Netspot is a kit for the preparation of Ga 68 dotatate, a new radiodiagnostic for evaluation of patients with neuroendocrine tumors (NETs) which is a rare and potentially life threatening disease. The preparation also requires the use of a Ga 68 generator which is not part of the drug.

(b) (4) as described in more detail in Section 7 of this document, the applicant has submitted a literature review with an attempted meta-analysis and the results of the study to which the applicant has obtained the right of reference (Study A). (b) (4)

There were no pre-specified and verifiable endpoints assessing a change in patient management in Study A or in any of the submitted publications. There was no well-defined standard of truth or reliably independent image assessment in most of the studies examined by clinical and statistical reviewers to assess diagnostic performance which would normally involve measurement of both sensitivity and specificity. There were no prospective protocols comparing diagnostic performance of PET using Ga 68 dotatate to SPECT using OctreoScan, an approved drug for disease localization in patients with NETs.

However, the new drug, Ga 68 dotatate prepared from Netspot is, like OctreoScan, a somatostatin analogue and is similar to it in its structure and the mechanism of action. The main technical difference is that Ga 68 dotatate is a PET drug with a shorter half-life providing greater imaging resolution and a shorter scan time which is obviously beneficial. The performance of Ga 68 PET in at least three of the reviewed studies appears to have been similar to that cited for OctreoScan in its labeling. Study A demonstrates a high level of agreement of Ga 68 dotatate PET with anatomic imaging, hence the ability to localize the disease, and the ability to localize the disease in some patients with negative OctreoScan SPECT. Studies B and C also appear to provide adequate evidence of disease localization by Ga 68 dotatate PET. Therefore one of the review conclusions is that (b) (4)

the submitted data are sufficient for achieving the claim of structural delineation, or visualization and localization, which would be of benefit to patients with NETs in potentially assessing the extent of their disease. The drug would also be of benefit to pediatric patients with somatostatin receptor positive tumors (see section 10).

The other conclusion is that this drug given as a single administration of a very small mass dose is safe from the standpoint of a risk of adverse reactions. Although an administered radioactivity dose is also quite small there is still a small risk associated with radiation exposure. Because the presence of somatostatin receptors is not limited to NETs there is also a risk of misdiagnosis and image misinterpretation. The quality of the Ga 68 dotatate injection prepared from Netspot has been thoroughly reviewed and further assured by bridging it to the product used for imaging in Study A.

Overall, the potential benefit of using Netspot to prepare Ga 68 dotatate and using such Ga 68 dotatate with PET imaging for localization of somatostatin receptor positive NETs in adults and pediatric patients appears to outweigh the negligible risk potentially associated with the use of this drug. Therefore CDTL assessment is in agreement with the multi-disciplinary review conclusions favoring the approval of Netspot for the indication recommended by the FDA.



Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> NETs are a rare mostly malignant tumors arising from neuroendocrine cells in a variety of tissues and presenting with variable clinical manifestations. NETs possess somatostatin receptors which can be imaged with radiolabeled somatostatin analogues such as Netspot proposed in the current application for preparation of Ga 68 dotatate, a new drug for PET imaging of NETs, or such as OctreoScan, a currently marketed SPECT drug for NET localization Somatostatin receptors could be present in other conditions NETs are mostly found in adults. In pediatric patients there are other somatostatin receptor positive tumors, like some neuroblastomas, which could also be imaged with Ga 68 dotatate PET. 	<ul style="list-style-type: none"> The disease is rare and potentially life threatening. There is no cure other than possible surgery. New treatments are being developed, some also based on the use of radioactive somatostatin analogues. Localizing and assessing the extent of the disease could help with a choice of therapy and prognosis Histopathological verification might be necessary Netspot could be also useful in pediatric patients.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> Current diagnostic imaging options for somatostatin receptor positive NETs include anatomical imaging and SPECT. The SPECT imaging is usually conducted after anatomical imaging. In patients who have poorly differentiated tumors FDG PET might be of use. The OctreoScan SPECT, the currently available alternative to Netspot PET, requires ~2 days for imaging and has poor resolution. 	<ul style="list-style-type: none"> The patient population will benefit from Netspot because the use of PET Netspot would result in lower radiation exposure compared to OctreoScan SPECT and would be associated with shorter scan time requirements and improved image resolution.
<u>Benefit</u>	<ul style="list-style-type: none"> The applicant conducted a literature review to support the use of the product and compared it to the currently approved product for the same indication and patient population. The number of articles is small, the number of patients is small, and the articles are not detailed nor are they prospective and blinded to meet the rigor of a traditional clinical trial. Two non-comparative articles from the same 	<ul style="list-style-type: none"> The totality of submitted evidence, including clinical data, mechanism of action and comparability to the approved product, support the use of Netspot as a complementary diagnostic imaging test for NET localization.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>single center appear to provide adequate evidence of disease localization by Ga 68 dotatate PET.</p> <ul style="list-style-type: none"> The clinical data from a study not yet published at the time of submission but to which the applicant had a right of reference were obtained on the basis of a protocol which was originally not intended for drug development. The study did demonstrate a high level of agreement of Ga 68 dotatate PET with anatomic imaging, hence the ability to localize the disease, and the ability to localize the disease in some patients with negative OctreoScan SPECT. Importantly, the quality of the product used in this study was bridged to the quality of the product which would be prepared using Netspot. Compared to the SPECT scan, the PET scan offers a decreased radiation dose to the patient, shorter duration of the imaging time, and greater image resolution. The product may provide information regarding the localization of the patient's disease that may not be noted on other imaging modalities (i.e. it is complementary to the existing diagnostic armamentarium). 	<ul style="list-style-type: none"> The patient may benefit from receiving previously unknown information about the extent of their disease and from lower radiation dose, shorter imaging time and greater image resolution.
<p><u>Risk</u></p>	<ul style="list-style-type: none"> There are ~1400 patients reported in the literature to have received Ga 68 dotatate. Unfortunately, the publications have not provided detailed reports of adverse reactions. The mass dose of the drug is sub-pharmacologic and the radiation dose is less than that of the approved SPECT product for the same patient population and indication. There are no adverse reactions found in the literature or in the VUMC clinical study experience associated with this drug. The articles reviewed for the pediatric population did not identify pediatric safety concerns. The product quality of Netspot was only assessed with the use of a specific model of a specific generator which is not part of kit. Only the Eckert and Ziegler GalliaPharma Ge 68/Ga 68 generator is recommended for use because an eluate other than the one from this generator has not been evaluated for sterility and radioactive germanium breakthrough. 	<ul style="list-style-type: none"> There is a small risk stemming from a radiation exposure which would be lower than from the currently approved drug. There is also a risk of misdiagnosis and image misinterpretation because the presence of somatostatin receptors is not limited to NETs. The risk of adverse reactions is negligible. There is no expectation that the risk profile will change in the post marketing setting. Netspot will be labeled for use only with Eckert and Ziegler GalliaPharma Ge 68 / Ga 68 generator.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk Management</u>	<ul style="list-style-type: none">• There are no unusual risk management issues at this time.	<ul style="list-style-type: none">• Product labeling• Routine pharmacovigilance

2. Background

The applicant has submitted NDA 208547 for a kit for the preparation of Ga 68 dotatate injection and proposed the following indication for use: [REDACTED] (b) (4)

[REDACTED] (b) (4). The DMEPA reviewers have recommended rejecting the originally submitted proprietary name, [REDACTED] (b) (4), and accepted Netspot instead.

During the review the team has determined that the submitted data were insufficient for providing substantial evidence of effectiveness for the proposed indication and informed the applicant of this in the 12/11/15 Discipline Review Letter. It was further stated in the Letter that [REDACTED] (b) (4) the data might support the drug's "potential utility in aiding the localization of tumors in patients with neuroendocrine tumors (NETs)." The clinical reviewer has also determined that the submitted evidence of effectiveness included patients with NETs from a variety of anatomic locations rather than [REDACTED] (b) (4). Therefore the indication for approval was changed to: *Netspot is indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.* Of note, back on 12/31/13, the product has received an Orphan designation as a diagnostic for the clinical management of NETs. The rationale for limiting the claim to tumor localization, rather than [REDACTED] (b) (4), as well as for extending it to pediatric patients is discussed further in sections 7 and 10, respectively.

NETs are a heterogeneous family of mostly malignant tumors that arise from neuroendocrine cells. The incidence of NETs in the US is estimated to be ~5 cases per 100,000 people. NETs are thought to be sporadic with undefined risk factors. The most common NET is carcinoid. Localization to small intestine and pancreas is common but may also involve stomach, lungs, thyroid and pituitary. NETs may also arise in the context of a syndrome of multiple endocrine neoplasms.

NETs are known to be capable of secreting various hormones and to carry hormonal receptors, somatostatin receptors (SSTR) in particular. Patients with NETs may or may not have symptoms of peptide secretion or mass effect. Diagnostic evaluation usually consists of laboratory tests (e.g. hormonal measurements) and anatomical imaging including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Endoscopy might be performed for GI symptoms or lesions. Isotope based Somatostatin Receptor Imaging (SRI) by means of Single Photon Emission Computed Tomography (SPECT) or PET, with a radiodiagnostic drug binding to a SSTR, would be usually conducted to localize and assess the extent of disease after a biopsy is obtained that suggests an NET. Once diagnosed, resection is the curative option. If surgery is not an option, therapy varies depending

upon location and type of tumor and may include somatostatin analogs, chemotherapy, or peptide receptor radiation therapy (PRRT) which is at the moment still investigational (a radiotherapeutic molecule here would be essentially the same as a radiodiagnostic, also binding to a SSTR, but carrying a therapeutic isotope).

NETs, especially when not undifferentiated, are known to be rich in SSTRs on their surface. There are five types of SSTR, with type 2 being the most common. Imaging of tumors rich in these receptors is based on the use of a variety of somatostatin analogues labeled with radioactive (photon or positron emitting) isotopes.

Indium-111 labeled octreotide (pentetreotide) is a radioactive somatostatin analogue approved in US and elsewhere as OctreoScan for SPECT imaging of NETs, specifically for “localization”.

OctreoScan is indicated for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.

Gallium 68 dotatate, the subject of the current NDA and similarly a somatostatin analogue, has been used as an investigational PET agent for the past 10 years, mostly in Europe and more recently in US. In comparison with the approved SPECT product, PET imaging with Ga68 dotatate has a series of advantages:

- Greater resolution of images - Ga68 dotatate PET has a 2-3 fold higher spatial resolution (3–6 mm vs. 10–15 mm)
- Stronger binding of the ligand to the target SSTR - affinity for SSTR2 of dotatate is ~ 10 x greater than that of pentetreotide
- Less radiation exposure to the patient - the effective radiation dose (exposure to patients) resulting from an administration of Ga 68 dotatate is much lower than that resulting from administration of In 111 pentetreotide. The effective radiation dose resulting from the administration of 150 MBq of Ga 68 dotatate to an adult weighing 75 kg is about 3.15 mSv as compared to 26 mSv resulting from 222 MBq dose of In 111 pentetreotide as approved for SPECT imaging
- Greater comfort and convenience for the patient - less time in the Imaging center- ~2 hour process for Ga 68 dotatate (Ga 68 half-life is 68 minutes) vs. ~2 day (!) process for OctreoScan due to longer half-life of In 111 (2.8 days)

Gallium 68 is a novel isotope and in addition to dotatate is used with other somatostatin analogues, such as dotatoc and dotanoc, for investigational PET imaging of NETs. There are multiple Investigational New Drug (IND) applications for these drugs, some with clinical trials and some with expanded access protocols.

As a radiodiagnostic, Ga 68 dotatate is regulated in accordance with 21 CFR 315 Diagnostic Radiopharmaceuticals. Ga 68 dotatate injection is a drug product which is prepared on-site in a radiopharmacy using a cold kit, such as Netspot, containing dotatate and a

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generator produced Ga 68. Ga 68 dotatate is a drug substance and Ga 68 is a radionuclide precursor. The generator producing Ga 68 is currently not considered to be a drug (nor is it a device from a regulatory standpoint) and its specific model has been reviewed as referenced by this application under a separate Drug Master File (DMF).

The existing regulations and guidances, among other things, address the possible indications for radiodiagnostic drugs and outline such categories as structural delineation, functional assessment, disease detection and patient management. A structural delineation claim would involve an ability to visualize or localize a structure and could be acceptable as long as such delineation is found to be clinically useful. This claim is usually being distinguished from a disease detection claim with the latter being thought of as a claim of diagnostic performance requiring a reliable assessment of such diagnostic categories as sensitivity and specificity.

The applicant has received feedback from the FDA after opening pre-IND 122818. FDA has advised the applicant that if there is not enough evidence in the literature to support the proposed claim the sponsor should carry out a clinical trial. The current application is a 505 (b)(2) application which relies on two sources of information: review of literature and clinical data from an expanded access study conducted at Vanderbilt University Medical Center (VUMC) to which the applicant has obtained the right of reference. VUMC has its own IND 111972 under which this study has been carried out.

The NDA 208547 has turned out to be a complex application from the standpoint of product chemistry and microbiology requiring multiple requests for additional information. The 2/12/16 submission was considered to be a major amendment extending the review clock by three months.

For Ga 68 dotatate prepared with the use of Netspot the recommended radioactivity to be administered by intravenous injection (bolus) is 2 MBq/kg of body weight (0.054 mCi per kg) but not more than 200 MBq (5.4 mCi). The proposed mass dose is less than 50 mcg.

As no safety issues have been identified with this micro-dose product during the review of the application, this CDTL summary will concentrate on product quality and effectiveness. No major disagreements have been encountered among the review disciplines.

The topics of product quality and effectiveness related to this NDA were the subject of CDER Regulatory Briefing on 2/05/16. The feedback received by the Division was consistent with the ongoing at the time preliminary review conclusions.

3. Product Quality

Netspot is supplied as a sterile, single-dose kit for the preparation of Ga 68 dotatate injection for intravenous use. As summarized in the CMC reviews and in the proposed product labeling, dotatate is also known as DOTA-0-Tyr3-Octreotate. It is a cyclic 8 amino acid peptide with a covalently bound chelator (dota).

Gallium 68 radionuclide is a precursor of the drug substance, Ga 68 dotatate, and is not supplied with the kit. In the case of this particular drug it is produced on-site by elution from an Eckert and Ziegler GalliaPharma Germanium Ge 68/Gallium Ga 68 generator and added to Netspot as part of the kit reconstitution and radiolabeling to produce the drug product, Ga 68 dotatate injection.

The kit includes the following components: Vial 1 (reaction vial with lyophilized powder) containing 40 mcg dotatate, 5 mcg 1, 10-phenanthroline, 6 mcg gentisic acid, 20 mg mannitol; Vial 2 (buffer vial) containing 60 mg formic acid, 56.5 mg sodium hydroxide and water for injection; and Accessory cartridge containing 660 mg porous silica used to [REDACTED] (b) (4).

As further stated in the review and the labeling, Ga 68 dotatate injection, after reconstitution and radiolabeling, also contains hydrochloric acid as an excipient derived from the generator eluate. The prepared Ga 68 dotatate injection for intravenous use, reconstituted from dotatate in the kit and radiolabeled with Ga 68 eluted from the generator (not supplied with the kit), is a sterile, pyrogen free, clear, colorless, buffered solution, with a pH between 3.2 - 3.8.

The data presented by the applicant show that dotatate in the kit is stable for at least 12 months when stored at the recommended temperature with the proposed container closure system. The identity of the reconstituted Ga 68 dotatate has been confirmed by comparison with a well characterized “cold” non-radioactive gallium dotatate reference standard. The product radiochemical purity is further confirmed by high performance liquid chromatography (HPLC) and instant thin layer chromatography (ITLC) analyses. The reconstituted drug product is stable for at least 4 hours when stored at 25°C.

In addition to product chemistry and microbiology data provided in the NDA, the review teams have also reviewed the DMF [REDACTED] (b) (4) from Eckert and Ziegler for GalliaPharma 68Ge/68Ga- generator manufactured in Berlin, Germany and specifically cited by the applicant. (The relevant Letter of Authorization has also been provided by Eckert and Ziegler to the applicant). Given that sterility, radioactive breakthrough and other quality characteristics vary from generator to generator and only this model has been reviewed and approved for use by the FDA, it would be important that at this time Netspot is approved for use only with this generator and this model.

One of the more challenging aspects of this application is that the proposed commercial formulation has not been used in any human clinical studies (or animal studies, for that matter). However, according to our CMC reviewers, the clinical formulation used by VUMC in IND 111972 clinical studies was compared to commercial formulation. The identity of the drug product of the two formulations has been established by physiochemical methods referenced to a characterized “cold” gallium dotatate. The two drug products have therefore been determined to be pharmaceutically equivalent.

Other review issues have involved characterization of various (b) (4) buffer components for reconstitution. The amount of gentisic acid proposed for use is consistent with the FDA Inactive Ingredient Guide, according to the primary CMC review. Although 1,10-phenanthroline is not listed in this guide and therefore represents a novel excipient, it is present at a very low level, with Pharmacology Toxicology (PT) reviewer finding its use acceptable. Another concern was the use of formic acid as a (b) (4). Although it can be a toxic solvent the amount of formic acid used here for the preparation of the drug product is below the permissible daily exposure according to the review. The level of formic acid was further evaluated by the PT reviewer and also found to be acceptable.

It should be noted that the CMC and product microbiology data submitted with these applications (the NDA and the DMF) consisted of multiple deficiencies requiring multiple information requests involving sterility, stability and even translations into English, among others. (Of note, the Microbiology reviewer’s original recommendation was to deny the approval). However, with the progress of the review all the necessary data have been presented and reviewed and found to be acceptable for approval.

The overall conclusion of the product evaluation is that the proposed commercial formulation has been bridged to the formulation used in the VUMC study and its quality confirmed and verified. The excipients in the formulation are used in very small and acceptable amounts. Therefore any differences in excipients between the proposed product and the products utilized in the literature would not impact drug performance, due to the small amounts of excipients and their nature. In addition, as pointed out by the reviewers, the strength of the proposed product is in the same range as the strengths of the drug products in the literature.

The Biopharmaceutics review team issued a bio-waiver for the proposed commercial formulation and the applicant’s claimed exclusion from environmental assessment was found to be acceptable. Facilities inspections have been completed and found no outstanding issues. The product review team has recommended the approval of the NDA.

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology reviewer has recommended approval. There are no safety signals. The in vitro binding studies evaluating somatostatin receptor binding across various somatostatin analogues including dotatate are described.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer has recommended approval. The clinical reviewer has summarized the Clinical Pharmacology review findings which are further excerpted here.

Dotatate is composed of a somatostatin analogue, Tyr3-Octreotate, linked to the metal chelator, DOTA which is the part of the molecule that gets radiolabeled with radionuclide Gallium 68 which is a positron emitter with the 68 min half-life.

Dotatate has a high affinity for and binds to cells that express the SSTRs, particularly SSTR2, that are overexpressed in neuroendocrine tumors. The product is administered in minute amounts (<50 mcg) and no pharmacologic action is expected. Peak tumor uptake is ~70 minutes post injection. Elimination is via the urinary system.

The radioactivity dose proposed for administration appears to have been based on experience described in a variety of publications. No dose finding studies have been submitted. The recommended radioactivity dose is quite small: 2 MBq/kg (0.054 mCi per kg) but not more than 200 MBq (5.4 mCi) as a total dose.

Organ dosimetry shows an increased uptake in spleen and some other organs. Uptake by uncinate process of pancreas may be seen in ~12% of patients.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

The primary clinical reviewer notes that the current application is for a New Molecular Entity (NME) with no prior US or foreign marketing experience. The clinical data come from the systematic literature review and the expanded access study conducted at VUMC. The primary statistical reviewer concentrated on the review of the attempted meta-analysis. The secondary and tertiary statistical reviews attempted to identify individual adequate and well controlled studies among the submitted clinical data.

Literature Review

The applicant conducted a literature search which returned 2378 publications of which 52 were selected for Clinical Overview and 13 publications (n = 579) were considered for meta-analysis in accordance with the pre-specified inclusion/exclusion criteria. The most common reasons for rejection were a different radiopharmaceutical, abstracts and reviews, non-clinical use and a small number of patients (< 10). The pre-specified primary endpoint was non-inferiority of performance characteristics of Ga68-Dotatate PET in comparison to OctreoScan. The secondary endpoint was non-inferiority of Ga68-Dotatate PET compared to OctreoScan for changes in patient management. Due to the small number of studies identified through the systematic review the meta-analysis on the pre-specified primary and secondary endpoints was not conducted. Only two publications compared the use of both drugs. Instead, the sponsor conducted an analysis measuring pooled sensitivity and pooled specificity. Five out of 13 publications lacked patient level performance measurements or involved investigational comparisons and were excluded from these analyses. VUMC data were included in pooling. As a result, nine studies were pooled for sensitivity and five were separately pooled for specificity. Of note, in addition to VUMC, data for both sensitivity and specificity were clearly provided in only two publications from the same single center. Pooled sensitivity was measured by the sponsor as 90% and pooled specificity - also as 90%. The review team did not agree with sponsor's methodology or clinical interpretation and has not relied on these analyses for consideration in the approval process. Instead, individual publications were reviewed in greater detail. Two publications where Ga68 dotatate was claimed to have been compared to OctreoScan and two publications where both sensitivity and specificity were measured have been found by the review team to be of particular interest and are being briefly addressed here. Adequately assessing both sensitivity and specificity in the same trial is important for control of bias in image interpretation.

Srirajaskanthan, et al (2010): The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPAoctreotide scintigraphy J Nuclear Med 51(6), 875-882.

Although listed by the applicant as a study comparing Ga68 dotatate performance to that of OctreoScan it is actually a retrospective study in patients with negative or "weakly-positive" In111-Pentreoctide scans. The PET images were interpreted by consensus between two readers blinded to the results of OctreoScan. Out of 51 such patients with a history of a histologically confirmed NET, 47 had

evidence of disease by conventional imaging or by biochemical markers both of which served as a standard of reference. In 41 of these, Ga68 dotatate scan was positive and in 6 patients it was falsely negative giving a “sensitivity” estimate of 87% in this select patient population. In 4 patients without evidence of disease by conventional imaging or by biochemical markers, Ga 68 dotatate scan was negative, and there were no false positive scans giving a ‘specificity” of 100% in this very small sample. These data are not adequate for evaluation of the test’s performance (retrospective design, poorly defined Standard of Truth, lack of independent blinded reads, small sample for specificity assessment) but do demonstrate its clinical utility. Based on the retrospective review, Ga68 dotatate imaging appears to have changed scheduled management in 36 patients, who were subsequently deemed suitable for PRRT. There were no clinical outcome data to confirm the appropriateness of the patient management changes. No details in relation to changes in management were provided.

Hofman, et al (2012): High management impact of Ga-68 DOTATATE PET/CT for imaging neuroendocrine and other somatostatin expressing tumors, Journal of medical imaging and radiation oncology 56(1), 40-47.

This was a study designed similarly to the one above. Out of 59 patients imaged with Ga68 dotatate, 40 had a previous OctreoScan. In 33 out of these 40, Ga68 dotatate provided additional information impacting clinical management. “Sensitivity” was based on 52 patients and measured as 100%. Specificity based on 7 patients was 86%.

In both of the above studies the terms “sensitivity” and “specificity” have to be used with caution because of the poorly defined standard of truth. Both studies are supportive of the Ga 68 dotatate ability to visualize NETs.

*Haug et al (2012): The Role of 68Ga-DOTATATE PET/CT in Suspected Neuroendocrine Tumors
J Nuclear Med 53:1686–1692 (Study B in the proposed labeling)*

In 104 patients (mean age 58; 52 men and 52 women) with suspected NETs due to clinical symptoms, elevated levels of tumor markers, or indeterminate tumors suggestive of NET, diagnostic performance of Ga68 dotatate PET in localizing tumor sites was retrospectively assessed using a truth standard: histopathology (n=49) or clinical follow up of up to 5 month duration (n=55). Images were interpreted by consensus between two readers who were not blinded to clinical information. NET sites were localized by truth standard in 36 patients (all by histopathology). Out of these, Ga68 dotatate was positive, correctly identifying an NET site, in 29 patients and was falsely negative in seven. In 68 patients with no NET identified by a truth standard, the scan was negative in 61 and falsely positive in seven patients.

Haug et al 2014: Neuroendocrine Tumor Recurrence: Diagnosis with 68Ga-DOTATATE PET/CT Radiology: Volume 270: Number 2:517 -525(Study C in the proposed labeling)

In 63 patients (mean age 58; 34 men and 29 women) being evaluated for NET recurrence (some undergoing surveillance which is not universally a part of current standard of practice), all with a truth standard as defined in the study above, the Ga68 dotatate images were interpreted by consensus between two local readers and independently by two off-site readers blinded to clinical information. Reader 1 correctly localized NETs in 23 out of 29 reference standard-positive patients and reader 2 correctly localized NETs in 22 such patients. In 34 patients with no NET identified by a reference standard, reader 1 was correct in 29 patients and reader 2 in 32.

Studies B and C, both from the same single center, are noted for a well-defined reference standard but limited by their retrospective design. Study B is further limited by its lack of blinded image interpretation. Of note, an error in image interpretation (false positives and false negatives) appears to have been similar in both studies. Given the limitations, the data from the studies might be reasonable for citation in the Clinical Studies section of the labeling [REDACTED] (b) (4). The data do appear to be adequate for a claim of tumor localization (visualization).

VUMC Study (Study A in the proposed labeling)

The study was designed as a “prospective, non-randomized, single center, open-label study comparing 68Ga-DOTATATE with conventional imaging including 111In-pentetreotide in Phase I/II diagnostic performance study”. However based on assessments by clinical and statistical reviewers the study appears to have been carried out as an expanded access study rather than as a clinical trial with pre-specified endpoint and analyses.

Out of 97 patients (mean age 54; 41men and 56 women) enrolled in the course of their clinical care and prospectively imaged with Ga68 dotatate PET scan, 78 were evaluable for comparing it to OctreoScan (i.e. the results of the latter was available and it was performed within the previous three years). Ga68 dotatate images were interpreted by consensus between two readers blinded to prior clinical information and compared to the results of anatomic imaging such as Computerized Tomography (CT) and/or Magnetic Resonance Imaging (MRI). Among 78 patients in whom CT and/or MR images and In 111 pentetreotide images were available, Ga 68 dotatate PET was in agreement with the CT and/or MR images in 74 patients (95%). Out of 50 patients with NETs localized by CT and/or MR imaging, Ga 68 dotatate was positive in 48 patients including 13 patients in whom In 111 pentetreotide was negative. Ga 68 dotatate was negative in 26 out of 28 patients in whom CT and/or MR imaging was negative.

While there is an apparent demonstration of added value of Ga 68 dotatate in comparison to OctreoScan [REDACTED] (b) (4)

Nonetheless, the study is supportive of Ga68 dotatate ability to visualize and localize tumors in patients with NETs.

Importantly, the GCP inspection conducted in the course of this NDA review cycle has concluded that the efficacy data from this study site reported in the NDA appear reliable. This is also the site selected for bridging the identity and quality of the to-be-marketed product (Netspot) to the identity and quality of the product prepared and used at this clinical site.

Efficacy summary

Based on review of the literature and on clinical data from VUMC and given the limitations in assessing sensitivity and specificity, the localization of NETs by Ga 68 dotatate appears to be at least comparable to that achieved by OctreoScan as cited in its labeling (accurate localization in about 86% of the patients). There are also studies where Ga 68 dotatate PET imaging has localized additional lesions or otherwise resulted in changing patient management. However there were no pre-specified endpoints to assess either diagnostic performance or patient management changes. The test's potential for providing false positive imaging data remains a concern. Nevertheless, given the totality of the efficacy data, the clinical and statistical reviewers have recommended approving Netspot for NET localization giving it a structural visualization claim.

8. Safety

Review of safety by the clinical reviewer has concluded that no safety issues are associated with possible adverse reactions to this product in this rare disease patient population. The review covered 97 patients from VUMC and about 1400 patients estimated to have been exposed to this drug in the literature. There were no reports of death or serious adverse events. Whereas no routine safety monitoring has been addressed in the literature no safety signals have been reported either. The VUMC patients have been more regularly followed with adverse event recordings and vital signs and, in a small subset, with laboratory examinations and EKGs. No safety events attributable to Ga 68 dotatate have been reported. No safety issues with this single administration micro-dose product are expected.

Of note, the GCP inspection of the VUMC site found some of the safety data to be missing and incompletely collected. However these violations have not affected the safety profile assessment of this drug.

9. Advisory Committee Meeting

No AC meeting has been held in connection with this application.

10. Pediatrics

NETs, a rare disease in adults, are exceedingly rare in children. However, some tumors that are more common in the pediatric age group, e.g. neuroblastomas (still a rare disease but not categorized as a NET) carry somatostatin receptors and therefore can be imaged with Ga 68 dotatate. The applicant has not included pediatric patients as part of the literature review and such patients were not included in the VUMC study. The clinical reviewer conducted an independent literature search addressing the use of Ga 68 dotatate PET in pediatric patients. The search returned three publications one of which was particularly helpful. It was a study of 30 pediatric patients (age 1 to 18 years old; 18 males, 12 females) with a mixture of tumors, mostly neuroblastomas and eight NETs. In 27 of these patients Ga 68 dotatate PET was successfully used to localize the disease. The dose chosen turned out to be equivalent to the dose proposed for adults in the current application. No adverse events were reported in any of the studies.

Therefore, the efficacy of Ga 68 dotatate PET imaging in pediatric patients with neuroendocrine tumors can be based on this published study of pediatric patients with somatostatin receptor positive tumors which included NETs. The efficacy can be further supported by the known ability of Ga 68 dotatate to bind to somatostatin receptors and by extrapolation from adult studies. The safety profile of Ga 68 dotatate, as limited as it is, appears to be similar in adult and pediatric patients with somatostatin receptor positive tumors. The recommended Ga 68 dotatate injection dose in pediatric patients can be weight based as in adults.

In response to the information request from the FDA, the applicant provided estimates of pediatric dosimetry expressing the risk of radiation exposure (effective dose) as a function of age and weight, comparing it to adults. Although the exposure is inversely proportional to age and weight the clinical significance is minimal because of the very small administered activity. Neither the applicant nor our reviewers were able to estimate pediatric organ dosimetry. Again, because of such a small overall dose, the lack of this aspect of dosimetry information would be of little clinical importance. It might be a consideration to obtain such data in the future.

11. Other Relevant Regulatory Issues

Netspot is eligible for New Chemical Entity exclusivity and possibly for Orphan exclusivity. Both will be determined after approval.

A clinical site inspection was conducted at VUMC for data integrity assessment and verification because these data were in part used to support the efficacy claim. No violations were found as far as the efficacy data were concerned. However a 483 was issued to the IND holder because of incomplete safety reporting. There was no impact on the review of this application.

12. Labeling

Prescribing Information

Both the Highlights and the Full Prescribing Information have undergone significant revisions including the Indication and product name (see section 2 of this document). The Dosage and Administration section has been completely re-written. The Clinical Studies section reflects the data from the studies supporting the indication of disease localization. Of note, the approved name is Netspot. FDA objected to spelling it as (b)(4). The applicant then used NETSPOT throughout the PI which is acceptable as per the Labeling Development Team.

At this time the labeling has not been finalized because of the ongoing internal discussion on how to describe in the labeling the use of the specific Ga 68 generator which is not a part of the drug being approved and with Ga 68 not being a drug itself but rather a drug precursor.

Other Labeling

The recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) have been incorporated in the revisions of the Carton and Container labeling as well as the PI. The review team has earlier agreed to the DMEPA recommendation on the Proprietary name. The Office of Prescription Drug Promotion (OPDP) has reviewed the labeling and found it acceptable.

13. Postmarketing Recommendations

Neither Risk Evaluation and Management Strategies (REMS) nor Postmarketing Requirements (PMRs) and Commitments (PMCs) are being considered at this time.

14. Recommended Comments to the Applicant

N/A

Cross Discipline Team Leader Review
NDA 208547 Netspot Ga68 Dotatate
Alex Gorovets MD 05062016

APPEARS THIS WAY ON ORIGINAL

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/s/

ALEXANDER GOROVETS
05/26/2016