CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208547Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	5/30/2016
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208547 0
Applicant	Advanced Accelerator Applications USA, Inc.
Date of Submission	7/01/2015
PDUFA Goal Date	6/01/2016
Proprietary Name / **Non-Proprietary Name**	NETSPOT Kit for the preparation of gallium Ga 68 dotatate injection
Dosage Form(s) / Strength(s)	Sterile lyophilized powder for injection, 40 mcg/10 mL vial. Sterile reaction buffer packaged separately as ~ 1 mL fill/10 mL vial. Single dose. After radiolabeling with
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Action/Recommended Action for NME:	Recommend approval
Approved/Recommended Indication/Population(s)	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.

APPEARS THIS WAY ON ORIGINAL

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Cynthia Welsh MD
Statistical Reviews	Satish Misra PhD, Jyoti Zalkikar PhD, and Thomas Gwise PhD
Pharmacology Toxicology Review	Ronald Honchel PhD
OPQ Reviews: Drug substance Drug Product, Environmental Assessment Process Facility Biopharmaceutics Microbiology Technical Lead	 Martin Haber PhD John Amartey PhD Dhanalakshmi Kasi PhD Krishna Gosh PhD Vidula Kohatkar PhD Helen Ngai PhD Eldon Leutzinger PhD
Clinical Pharmacology Review	Christy John PhD
CDTL Review	Alex Gorovets MD
Labeling Review	Michele Fedowitz MD, Nushin Todd MD, PhD
OPDP	Adam George PharmD
OSE/DMEPA	Michelle Rutledge PharmD
OSE/DRISK	Naomi Redd PharmD
OSI/DCCE/GCPAB	John Lee MD

OND = Office of New Drugs
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Prom.
CDTL= Cross-Discipline Team Leader
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific Investigations
GCPAB = Good Clinical Practice Assessment Branch
DCCE = Division of Clinical Compliance Evaluation
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Accurate detection and staging of neuroendocrine tumors is important for patients' management and improved outcomes. NETSPOT is a radiopharmaceutical kit consisting of an organic ligand (DOTATE) and excipients to which a radionuclide ($^{68}GaCl_3$) is added to form a radiolabeled ligand (gallium Ga 68 dotatate, the drug substance), in a formulation suitable for injection. The $^{68}GaCl_3$ is obtained from a GalliaPharm radionuclide generator provided separately.The organic ligand contains a peptide designed to bind to somatostatin receptors; the receptors are overexpressed in most neuroendocrine tumors. The radionuclide Ga 68 decays with the emission of positron that can be imaged by positron emission tomography (PET). The Applicant (Advanced Accelerator Applications) proposed Ga 68 dotatate PET imaging for use in (b) (4) *patients with NETs* (b) (4) *FDA determined that the clinical experience supports the clinical utility of the product for locating NET in all patients with somatostatin-receptor positive NETs. The efficacy of Ga 68 dotatate was evaluated in three open label single center studies.* Suboptimal *study design, image interpretation procedures, and study conduct, and the lack of patient level data are important shortcomings in the studies.*

In one study 97 adults with known or suspected NETs received Ga 68 dotatate scans. The scans were interpreted independently by two blinded readers and compared to CT and/or MR and to In 111 pentetreotide SPECT scans. Among the 78 patients with available CT and/or MR and SPECT scans, Ga 68 dotatate PET was in agreement with the CT and/or MR scans in 74 patients. Among 50 patients with NETs localized by CT and/or MR, 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.

In a second study of 104 patients with suspected NETs, Ga 68 dotatate PET localization of tumor sites was assessed using a reference standard. Scans were interpreted by consensus between two unblinded readers. NET sites were localized in 36 patients all by histopathology. Ga 68 dotatate was positive in 29 patients and falsely negative in seven. In 68 patients with no NETs identified the scans were negative in 61 patients and falsely positive in seven.

In a third study 63 patients were evaluated for NET recurrence using a reference standard as described for the study above. Ga 68 dotatate scans were interpreted independently by two blinded readers. 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 NETs identified by a reference standard, reader 1 was correct in 29 patients and reader 2 in 32.

The risks of Ga 68 dotatate are associated with radiation exposure and with image interpretation errors. The use of the product contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Incorrect image interpretation is possible because Ga 68 dotatate uptake is not specific for NETs. Clinical correlation, which may include histopathological evaluation of the suspected site, is recommended. No serious adverse reactions have been identified in the three studies and in the published literature. Given the clinical importance accurate detection of neuroendocrine tumors, the risks are acceptable.

I conclude that the risk benefit of Ga 68 dotatate is favorable and recommend approval of this new drug application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NETs are heterogeneous tumors derived from embryonic neural crest tissue and represent 0.5% of all malignancies with a population prevalence of 2-6/100,000. NETs are found primarily in the GI tract, tracheobronchial tree, and adrenal medulla; many other anatomic sites can be affected. Conventional imaging may fail to detect primary tumors and provided incomplete information about metastatic spread. • Development of new diagnostics is affected by the rarity of the condition.	Accurate detection of NETs is an important need for improved patients' management and clinical outcomes.
Current Treatment Options	• Magnetic resonance imaging, computed tomography, ultrasonography, single photon emission tomography using In 111 pentreotide and positron emission tomography are imaging procedure that are performed to localize NETs • The diagnostic accuracy of available imaging for tumor detection is suboptimal. Studies are needed to evaluate comparative efficacy of imaging procedures for tumor staging and patient management.	The standard imaging modalities have limitations. New diagnostic options are needed for this serious condition. Diagnostic performance characteristics and value of radiopharmaceuticals in patient management need to be established.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The data from three single-center studies provided adequate evidence of the utility of Ga68 dotatate for detection of NETs • Accurate staging of NET is an important medical need. (b) (4) [redacted] • The studies were not adequately designed to evaluate comparative performance of radiopharmaceuticals.	The totality of the evidence consisting of the prospective and retrospective clinical studies, binding affinity of the organic ligand to its pharmacologic target, favorable background clearance after administration of the drug substance, potential for higher resolution characteristics, establish the utility of the drug.
Risk	• Radiation exposure and misinterpretation of clinical images, are the most important safety concerns. • Ga 68 dotatate contributes to a patient overall radiation exposure. Long term cumulative exposure increases the risk of cancer. • The effective radiation absorbed dose is similar or lower than that of comparable radiopharmaceuticals.	The risks are generally low and consistent with a radiopharmaceutical whose pharmacophore is administered in subpharmacologic doses. .

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Imaging results need to be verified by additional clinical testing including histology; the labeling will address this risk.
Risk Management	• Diagnostic imaging agents as a class do not pose clinical risks that warrant the use of postmarketing risk management procedures.	No action is needed

2. Background

On September 28, 2015 the Applicant (Advanced Accelerator Applications USA Inc.) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act a new drug application (NDA) for the new molecular entity Ga 68-DOTATATE Injection, 40 mcg/vial. On February 12, 2016, FDA received a major amendment to this application. Therefore FDA extended the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 1, 2016.This diagnostic radiopharmaceutical is proposed for use in PET imaging for (b) (4) patients with neuroendocrine tumors. This review summarizes my assessment of the approvability of the NDA.

NETSPOT is a radiopharmaceutical kit consisting of an organic ligand and excipients to which a radionuclide is added to form a radiolabeled ligand, the drug substance, in a formulation that is stable and suitable for injection. The radionuclide ($^{68}GaCl_3$) is obtained from a ^{68}Germanium/^{68}Gallium (^{68}Ge/^{68}Ga) radionuclide generator; the generator is provided separately. The drug substance is Ga 68-DOTA-d-Phe- -Tyr-d-Trp-Lys-Th-Cys-Thr (cyclo 2,7) and is also designated as Ga 68-DOTATATE. Verification that the drug substance is formed on radiolabeling NETSPOT is performed at the point of release through quality control testing of the patient dose in the nuclear pharmacy. The product is manufactured by Gipharma S.r.l. and will be distributed by Advanced Accelerator Applications USA.

The primary clinical reviewer (Dr. Welsh) and the cross discipline team leader (Dr. Gorovets) provide an extensive discussion of the necessity of new diagnostic imaging options for patients with neuroendocrine tumors (NETs). NETs are heterogeneous tumors derived from embryonic neural crest tissue and represent 0.5% of all malignancies with a population prevalence of 2-6/100,000. NETs are found primarily in the: GI tract, tracheobronchial tree, and adrenal medulla; many other anatomic sites can be affected. NETs express somatostatin receptors and somatostatin analogues are important molecules for the diagnosis and therapy for these tumors.

Somatostatin receptor imaging (SRI) for NET localization is designed to make use of two different imaging platforms and radiopharmaceutical production technologies. These technologies consist of

- single photon emission tomography (SPECT) characterized by greater accessibility, lower cost, numerous approved radiotracers, ease of final product preparation and
- positron emission tomography (PET) with the potential for higher resolution, speed, but generally requiring more complex radiochemistry.

The first SRI SPECT agent 111In-pentreotide was approved in 1994. Advances in Ga 68 radiochemistry have sparked interest in PET SRI.

Dr. Gorovets summarizes the advantages of Ga 68 based SRI due to lower radiation exposure and more favorable background clearance allowing for more rapid image acquisition.

The patent for the pharmacophore dotatate expired in 2015. It appeared that marketing prospects might not be sufficient to generate robust commercial interest because of the relatively small size of the patient population and the anticipated limited use of an agent intended for evaluation in these

patients. In public scientific meetings academic investigators and patients advocates also raised concerns about what they perceived as uncertain prospects for reimbursement by third-party payers and lack of funding for prospective multicenter studies.

Published studies appeared to support the potential for Ga 68 dotatate to provide an important alternative to available imaging tests. For this reasons FDA encouraged the use of expanded access protocols at single centers to make the drug available under IND and to generate verifiable data. FDA encouraged stakeholders to pursue a 505(b)(2) NDA supported by a systematic review of published studies and by prospective clinical experience. FDA also encouraged manufacturers of the commercially $^{68}Ge/^{68}Ga$ radionuclide generators to prepare drug master files and pointed out the need to bridge clinical trials products used in the scientific literature to proposed commercial product. Consistent with previous regulatory history, FDA anticipated that a radiopharmaceutical kit manufacturer might be the Applicant for an eventual new drug application.

Advanced Accelerator Applications USA, Inc. submitted this NDA 208547 for NETSPOT as a 505(b)(2) application supported by the literature and by the retrospective adaptation of clinical experience developed at Vanderbilt University Medical Center (VUMC), from an expanded access protocol aiming to assess the clinical utility of the investigational agent for use in the management of patients with NET. The Applicant acquired the rights to the data and did not conduct new preclinical studies or new clinical trials.

The application was granted a priority review status because Netspot was judged to have the potential to improve the diagnostic accuracy for a serious condition for which an accurate diagnosis is critical for patient management and improved outcome. The product also received Orphan designation for the proposed use as a diagnostic for the clinical management of NETs.

The Primary clinical reviewer (Dr. Welsh) and the cross discipline team leader (Dr. Gorovets) provide an overview of the public health importance of the clinical condition, namely neuroendocrine tumors. Standard imaging modalities for evaluation of NETs have generally low accuracy. The clinical reviewers summarize the available diagnostic options including the radiopharmaceutical indicated for use in this patient population. OctreoScan (In 111 pentreotide) is a single photon emission computerized tomography (SPECT) agent approved in 1994 for use for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.

There were no major scientific disagreements with the Applicant. The Applicant provided additional data to satisfy a number of information requests. There was agreement among all the primary and secondary reviewers regarding the overall adequacy of quality and preclinical information.

The efficacy study design considerations and analyses are typical for diagnostic medical imaging products. There are no class effects of particular concern for the product. No non-clinical safety signals, novel or incompletely resolved safety concerns were identified. No postmarketing requirements and no risk evaluation and mitigation strategies are needed.

The clinical benefit of the product is the ability to localize NETs. (b) (4) No conclusions are possible with regard to performance of the product relative to the currently approved product OctreoScan

from either the scientific literature or from the expanded access program at VUMC.

I concur with the unanimous recommendation for a regulatory action of approval of the NDA made by all the review disciplines.

3. Product Quality

The proposed USAN name for the product is gallium Ga 68 dotatate. The proprietary name is NETSPOT. Netspot is a radiopharmaceutical kit, consisting of the following components.

- Vial #1 (designated reaction vial with lyophilized powder) contains (b) (4) DOTA-Tyr3-Octreotate (40 mcg), and the excipients 1.10-Phenanthroline (5 mcg), (b) (4) Mannitol (20 (b) (4)), Gentisic acid (6 mcg) (b) (4) and nitrogen
- Vial #2 (designated buffer vial) contains Formic Acid (60 mg), Sodium Hydroxide (56.5 mg) and water for injection
- Accessory cartridge contains porous silica (660 mg) and is intended to reduce the amount of Ge 68 in the eluate

The drug substance is Ga 68-DOTA-d-Phe- Tyr-d-Trp-Lys-Th-Cys-Thr (cyclo 2,7) also designated as Ga 68-DOTATATE. The kit is used to prepare the drug substance as follows. The needed volume of Vial 2 (buffer vial) is added to Vial 1 (reaction vial). The required $^{68}Ge/^{68}Ga$ generator (provided separately to a nuclear pharmacy) is attached to Vial 1 through the accessory cartridge and $^{68}GaCl_3$ is eluted . Vial 1 designated the reaction vial is heated to radiolabel DOTATATE (b) (4) At the end of radiolabeling, Vial 1 contains the drug substance. The vial is cooled and the patient dose is subjected to quality control.

I concur with the assessment made by product quality reviewers that all the drug quality aspects, i.e. the Drug Substance, Drug Product, Microbiology, Process, Facilities, Biopharmaceutics, and Environmental Assessment have been fully reviewed and are adequate to support approval of this new drug application. I concur with the assessment by the quality discipline reviewers that all the issues identified during the application review have been addressed, that the product labeling provides adequate instructions for preparation and administration, and that no postmarketing commitments or risk management steps are necessary.

The application quality lead (Dr. Leutzinger) provides an integrated quality assessment focused on the critical quality attributes of the product. Dr. Leutzinger lists all the issues identified by the various discipline reviewers, summarizes the principal technical considerations and describes their resolution. The principal quality issue for radiopharmaceutical kits is the verification that the drug substance Ga 68-dotatate, is formed on addition of $^{68}GaCl_3$ to NETSPOT.

I agree that the formulation of the proposed product and the formulation of the products in the clinical studies are comparable. The product quality reviewers made a finding of comparability based on the following main data considerations.

- the drug substance is the same as the "cold" Ga-dotatate reference standard
- the differences in excipients do not affect drug performance because of small amounts and

similarity to excipients used in other radiopharmaceuticals
- the strength of the proposed product is within range as the strengths of the drug products in the literature.

The $^{68}Ge/^{68}Ga$ generator presents another consideration, critical to assurance that when $^{68}GaCl_3$ is added to NETSPOT, the pharmaceutical quality of the final drug product is assured. None of the commercially available generators in the US are approved. The Applicant designates the Eckert & Ziegler $^{68}Ge/^{68}Ga$ generator for use with NETSPOT. The Agency determined that since the generator eluate is not proposed for use as a finished drug product the generator does not meet the requirement for regulation as a drug. Therefore for this application the regulatory pathway is through a drug master file (DMF).

The critical quality attributes of the generator are: the retention of the parent radionuclide on the generator column i.e. control of Ge 68 "breakthrough" in the eluate, and elution efficiency i.e. strength of Ga 68 in the eluate. These attributes are met (see DMF # (b) (4) review). I agree that to provide the needed quality assurance, the labeling needs to cite the name of the Eckert & Ziegler generator (GalliaPharm).

I concur with the assessment by Dr. Haber that the drug substance data are adequate. I reference the drug product review by Dr. Amartey who identified and verified the components, compositions, and functions of the kit and of the final product. I agree that the use of alternate radionuclide generators is not supported by the information provided in the application. I concur with the assessment that the identity of the drug product of the commercial formulation and clinical studies formulations has been established by physiochemical methods referenced to a characterized "cold" [natGa]-DOTATATE. The two drug products are therefore pharmaceutically equivalent.

I reference the drug product manufacturing review By Dr. Kasi and agree that the process parameters and material attributes for the product are adequate.

I agree with the conclusion by the biopharmaceutics reviewer Dr. Kolhatkar that the Applicant's biowaiver request be granted. The reviewer determined that the differences in excipient composition between the proposed drug product and the previously used formulation are not material because those excipients do not interact directly with the drug substance and are not expected to influence the in vivo disposition and clinical performance of the Ga 68-DOTATATE. The reviewer considered that the proposed product contains 1,10-phenanthroline and gentisic acid (b) (4) and mannitol (b) (4). The reviewer determined that the excipients are not expected to impact the in vivo disposition of the drug product. The pH specification for the proposed product and the clinical study products are in the acidic range. Any possible slight differences in the protonation equilibria of the most acidic functional groups of DOTATATE molecule in solution will disappear after administration, when the drug comes in t contact with the blood.

I concur with the assessment of the facility reviewer Dr. Gosh that all the manufacturers are in conformity with good manufacturing practices to assure that the product meets the safety, identity, strength, and purity requirements. The key raw materials for manufacturing the drug substance prepared by the nuclear pharmacy form a complex supply chain for the product kit. Since the final drug product is not purified after radioactive labeling the raw materials and excipients manufacturing and control strategy was an important focus for the inspections of the facilities. All facilities were considered acceptable

I concur with the finding by Dr.Ngai that sufficient sterility assurance has been provided. The

PET drug product is a sterile unpreserved solution for intravenous administration. There are no ununresolved microbiology deficiencies. The drug product is a sterile 2-vial kit which consists of a sterile lyophilized powder for reconstitution and a sterile reaction buffer. The lyophilized powder is sterile filtered and aseptically filled while the reaction buffer is subject to (b) (4) The reaction buffer is (b) (4) The accessory cassette is sterilized (b) (4).

4. Nonclinical Pharmacology/Toxicology

I concur with the recommendation by the pharmacology/toxicology reviewer Dr. Honchel that the application be approved based on adequate nonclinical safety evaluations and the safety profile for the intended use. Dr. Honchel relied on preclinical studies conducted with cold Lutetium (^{175} Lu) DOTATATE for the assessment of preclinical safety.

No animal studies on fertility, embryology, mutagenic potential, or carcinogenic potential have been conducted with Ga 68 dotatate and none were necessary. In vitro genotoxicity did not show evidence of mutagenesis.

Pharmacology
The IC50s for various somatostatin analogues was evaluated in vitro using membranes prepared from CA20948 tumors. DOTATATE exhibited the highest affinity (0.48 nM) including DTPA-octreotide (2.5 nM).

Safety pharmacology
In hERG assays, ^{175}Lu-DOTATATE (100 mcM) did not induce a significant reduction in hERG current. In a rat neuro safety pharmacology study. ^{175}Lu-DOTATATE at doses up to 20 mg/kg (~4800-fold safety factor based on the HED) did not induce drug-related effects. In a dog cardiovascular safety pharmacology study ^{175}Lu-DOTATATE (40-800 mcg/kg) had no effects on ECG or body temperature and induced increases in systolic, and diastolic arterial blood pressures with associated bradycardia. In a rat respiratory safety pharmacology study there were no drug-related effects on respiratory parameters observed at the 1.25 mg/kg dose level (~300-fold safety factor based on the HED).

General toxicology
In a rat IV repeat-dose toxicity study, vehicle, 1.25, 5.0, or 20 mg/kg ^{175}Lu-DOTATATE was administered every 2 weeks for 42 days. An increased incidence in pancreatic acinar apoptosis was observed in the high dose groups that had not completely reversed by the end of the recovery period. The NOAEL was 5.0 mg/kg (~1200-fold safety factor based on the HED). In a dog IV repeat-dose toxicity study up to 3.2 mg/kg of ^{175}Lu-DOTATATE no drug-related adverse effects were observed in this study (~2600-fold safety factor based on the HED).

5. Clinical Pharmacology

I concur with the recommendation by the clinical pharmacology reviewer Dr. John that the application be approved. The following is a summary of Dr. John's findings.

Mechanism of action. Ga 68 dotatate binds to somatostatin receptors, with highest affinity for

subtype 2 receptors (SSTR2). The pharmacophore binds to cells that express somatostatin receptors including malignant cells, which overexpress these receptors. The radionuclide Ga 68 is a positron emitter suitable for PET imaging

Pharmacodynamics. The product does not induce pharmacologic effects. The relationship between Ga 68 dotatate plasma concentrations and successful imaging was not evaluated.

Pharmacokinetics. Pharmacokinetics in blood have not been performed. Ga 68 dotatate distributes to all sstr2- naturally expressing organs and to sstr2 positive tumors.

Dose. The recommended dose is 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4mCi) administered as intravenous bolus injection. These doses are consistent with the VUMC trial and literature data. No dose finding studies were submitted and none appear in the literature

Dosimetry. The effective radiation dose resulting from the administration of 150 MBq to an adult weighing 75 kg, is about 3.2 mSv. The corresponding radiation dose to the critical organs, which are the urinary bladder wall, the spleen and the kidneys/adrenals, are about 18, 16 and 12 mGy, respectively.

Drug interactions. Non-radioactive somatostatin analogs used in therapy competitively bind to the same somatostatin receptors as Ga 68 dotatate. The labeling will recommend imaging patients with Ga 68 dotatate PET just prior to dosing with long-acting analogs of somatostatin. Short-acting analogs of somatostatin can be used up to 24 hours before imaging with Ga 68 dotatate.

6. Clinical Microbiology

This section is not applicable to radiopharmaceuticals intended for diagnostic use.

7. Clinical/Statistical-Efficacy

I concur with the clinical and statistical reviewers' assessment that the evidence provided in the application (b) (4) . I also concur with the review teams' assessment that that the evidence supports the use of the product for locating neuroendocrine tumors. Moreover, the available data supports (b) (4) the patient population to all somatostatin-receptor positive NETs.

There is general agreement that the efficacy of Netspot is established in three open label single center studies that are summarized below. However, I agree with the assessment by the reviewers that suboptimal study design, image interpretation procedures, and study conduct, and the lack of patient level data are important shortcomings in the studies.

I concur that diagnostic performance based on meta-analyses of the studies published in the literature is not reliable and cannot be used for regulatory decision making. The uncertainties in the estimates of diagnostic performance also apply to the use of another diagnostic radiopharmaceutical; no comparative efficacy assessments are therefore possible. The three clinical studies cited in the labeling are summarized below.

In the VUMC study, 97 adult patients with known or suspected NETs received Ga 68 dotatate scans. The scans images were interpreted independently by two readers blinded to clinical information and were compared to CT and/or MR and to indium In 111 pentetreotide SPECT scans. In 78 patients with available CT and/or MR and SPECT scans, Ga 68 dotatate PET was in agreement with the CT and/or MR scans in 74 patients. Among 50 patients with NETs localized by CT and/or MR, 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.

In a retrospective study of 104 patients with suspected NETs performance of Ga 68 dotatate PET in localizing tumor sites was assessed using histopathology (n = 49) or clinical follow up of up to 5 month duration (n = 55). Scans were interpreted by consensus between two interpreters not blinded to clinical information. NET sites were localized in 36 patients all by histopathology. Ga 68 dotatate was positive in 29 patients and falsely negative in seven. In 68 patients with no NET identified the scans were negative in 61 patients and falsely positive in seven.

A third study in 63 patients evaluated for NET recurrence used a reference standard as described for the study above.. Ga 68 dotatate scans were interpreted independently by two blinded readers. 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.

8. Safety

I concur with Dr. Welsh's assessment that in the intended population and clinical use, the experience reported in the three single-center studies and in a survey of the scientific literature is adequate to assess the safety of Netspot. No deaths or serious adverse reactions were reported.

The risks of Netspot are associated with radiation exposure and with image interpretation errors. Netspot use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. All radiopharmaceuticals, including Ga 68 dotatate have the potential to cause fetal harm.

The uptake of Ga 68 dotatate reflects the level of somatostatin receptor density in NETs. However, uptake can also be seen in a variety of other tumor types (e.g. those derived from neural crest tissue). Increased uptake might also be seen in other pathologic conditions (e.g. thyroid disease or subacute inflammation) or might occur as a normal physiologic variant (e.g. uncinate process of the pancreas). The uptake Ga 68 dotatate may need to be confirmed by histopathology or other assessments.

9. Advisory Committee Meeting

The application did not raise precedent- setting regulatory or scientific issues. For this reasons no advisory committee meeting was necessary. On February 5, 2015 DMIP discussed the present application was at a regulatory briefing in the Office of New Drugs. The approach to bridging the commercial product with the product used in the clinical studies was judged to be acceptable and

the totality of the available evidence in support of the use of the product for localization of neuroendocrine tumors was considered to be adequate.

10. Pediatrics

The efficacy of Ga 68 dotatate PET imaging in pediatric patients with neuroendocrine tumors is based on extrapolation from adult studies, from studies demonstrating the ability of Ga 68 dotatate to bind to somatostatin receptors, and from a published study of Ga 68 dotatate PET imaging in pediatric patients with somatostatin receptor positive tumors. The safety profile of Ga 68 dotatate is similar in adult and pediatric patients. The recommended Ga 68 dotatate injection dose in pediatric patients is weight based as in adults.

11. Other Relevant Regulatory Issues

I concur with the assessment by the reviewer from the Division of Medication Error Prevention and Analysis. Dr. Rutledge and the recommendations made to improve the readability and prominence of important product information such as strength and route of administration and provide for adequate differentiation between the two vials included in the kit. These recommendations were incorporated in the labeling.

I concur with the assessment of the reviewer from the Office of Prescription Drug Promotion. Dr. Adam reviewed the final versions of the prescribing information and the carton and container labeling and found them to be acceptable.

I concur with the assessment by Dr. Lee of the Office of Scientific Integrity. The OSI conducted an on-site GCP inspection of the VUMC study with emphasis on PET image interpretation and internal (IRB) study monitoring. Case records were reviewed for all 97 subjects enrolled in the study. A detailed review was performed for 22 subjects (17 with discordant PET results and five others selected at random).Verification of NDA data included the 17 read results discordant between PET and SPECT.

The efficacy data from this study site reported in the NDA was judged to be reliable. Audited efficacy data were adequately verifiable among source records, DCFs, and NDA data listings. However, some of the protocol-specified safety assessments required under this investigator's IND were not collected or documented. A Form FDA 483 was issued for these protocol deviations related to safety monitoring. I attribute the missing safety data to the consequences of the expanded access protocol. I do not view the missing data as affecting the assessment of the safety of the product because of the lack of safety signals from numerous published studies.

I concur with assessment by DMEPA and by the NDA review team that the proposed proprietary name, NETSPOT is acceptable.

I concur with the recommendation by Dr. Redd. 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

12. Labeling

The following is a summary of the consensus views of the review team and reflects the input by Drs. Todd and Fedowitz who led the review of the labeling for content and consistency with the regulations.

- INDICATIONS AND USAGE section:
  The FDA reviewers proposed a visualization claim and (b) (4) the indicated population to include pediatric patients and patients with somatostatin receptor positive NETs without restriction to location..
  .
- DOSAGE AND ADMINISTRATION section:
  The recommended dose is effective. However no dose ranging studies were performed to optimize the Netspot dose. The radionuclide generator reviewed is specified by name. The requirement for periodic testing of eluate for 68 Ge break-through was added along with the specification (< 0.001%).

- WARNINGS AND PRECAUTIONS sections:
  The principal risks associated with Netspot are due to radiation absorbed dose from the Ga 68 radioisotope and errors in image interpretation. These risks are described in the warnings section.

13. Postmarketing

The applicant did not submit a proposed risk management plan with this application. A risk evaluation and mitigation strategy for this new molecular entity is not necessary to ensure the benefits of this product outweigh its risks. As a class, diagnostic radiopharmaceuticals have not required such a strategy for approval.

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/s/

LIBERO L MARZELLA
05/31/2016