

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208547Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA 208-547

Submission Date: July 1, 2015 (SDN 1)
October 26, 2015 (SDN 14)

Brand Name: (b) (4) (Kit for the Preparation of ⁶⁸Ga-DOTATATE for Injection)

Formulation: Lyophilized powder for reconstitution

OCP Reviewer: Christy S John, Ph.D.

OCP Team Leader: Gene M. Williams, Ph.D.

OCP Division: Division of Clinical Pharmacology V

OND Division: Division of Medical Imaging Products

Applicant: Advanced Accelerator Applications USA, Inc.

Submission Type; Code: Original-1 (Type 1- New Molecular Entity)

Dosing regimen: For PET imaging in adults: The recommended radioactivity to be administered is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) not more than 200 MBq (5.4 mCi) via intravenous administration

Indication:

(b) (4)

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1 EXECUTIVE SUMMARY

Advanced Accelerator Applications has submitted NDA 208-547 for $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for (b) (4)

This application relies on data from a clinical study conducted by Vanderbilt University Medical Center (VUMC) and clinical trials from the literature.

$^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ has high affinity for somatostatin subtype 2 receptors (SSTR₂). It binds to cells that express somatostatin receptors including malignant cells, which overexpress SSTR₂ receptors.

The earliest trials studied doses ranging from 80 to 200 MBq. The basis for selecting these doses does not appear in the submission or in the literature. No dose finding studies were submitted and none appear in the literature. The proposed package insert dose is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) not more than 200 MBq (5.4 mCi). These doses are consistent with the VUMC trial and the literature data.

The sensitivities and specificities of $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ PET/CT and $^{111}\text{In-pentetreotide}$, an agent approved by FDA for imaging SSTR positive tumors using SPECT, were compared in the VUMC trial (n=78). Sensitivities of $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and $^{111}\text{In-pentetreotide}$ were 96.0% (95% CI: [86.3%; 99.5%]) and 72.0% (95% CI: [57.5%; 83.8%]), respectively, and specificities were 92.9% (95% CI: [76.5%, 99.1%]) and 89.3% (95% CI: [71.8%, 97.7%]), respectively.

About 12% of injected radioactivity is excreted in urine in first 4 hours. There is no information on drug biodistribution/PK in patients with hepatic or renal impairment in the submission.

The effective radiation dose (exposure to patients) resulting from the administration of $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ PET is much lower than that resulting from administration of the approved agent $^{111}\text{In-pentetreotide}$. The effective radiation dose resulting from the administration of 150 MBq for an adult weighing 75 kg, is about 3.15 mSv as compared to 26 mSv for the 222 MBq dose approved for $^{111}\text{In-pentetreotide}$.

There are no data on PK parameters and how they change with intrinsic factors. While pediatric data are not available, a pediatric waiver is not required as $^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the current indication has been granted Orphan drug designation.

Non-radioactive somatostatin analogs competitively bind to SSTR₂. The package insert recommends avoiding concomitant treatment with long acting analogs of somatostatin (b) (4) prior to the imaging exam, and short acting analogs for 24 hours prior.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 208-547 and recommends approval of the application.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
<p>Proposed text for Dosage and Administration:</p> <p>(b) (4)</p>	<p>Yes</p> <p>Refer to Sections 2.2.5, and 2.2.9</p>	<p><u>Labeling Recommendation:</u> No change to applicant's proposal.</p>
<p>Proposed text for Drug Interactions: Non-radioactive somatostatin analogs competitively bind to the same somatostatin receptors (b) (4)</p> <p>(b) (4)</p> <p>long acting analogs of somatostatin (b) (4)</p> <p>Short acting analogs of somatostatin can be used up to 24 hours before (b) (4) imaging (b) (4)</p>	<p>Yes</p> <p>Refer to Section 2.4.7</p>	<p><u>Labeling Recommendation:</u> Minor edits to applicant's language, no change to substance.</p>
<p>No dosing adjustment is recommended for any intrinsic or extrinsic factor</p>	<p>Yes</p> <p>Refer to Sections 2.3.2</p>	<p><u>Comment:</u> No change to applicant's proposal.</p>

Labeling Recommendations

Refer to Section 3 DETAILED LABELING RECOMMENDATIONS.

1.2 Post-Marketing Requirements and Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Advanced Accelerator Applications has submitted New Drug Application (NDA) 208547 for ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate for (b) (4)

This NDA application relies on data from a clinical study conducted by Vanderbilt University Medical Center (VUMC) and clinical trials from the literature.

DOTA⁰-Tyr³-Octreotate is an eight amino acid peptide with that has high affinity for somatostatin subtype 2 receptors (SSTR₂). It binds to cells that express somatostatin receptors, including malignant cells which overexpress SSTR₂ receptors.

Efficacy

The clinical endpoints were sensitivity and specificity. The performance of of ⁶⁸Ga-DOTATATE PET/CT was compared to that of ¹¹¹In-pentetreotide, an agent approved by FDA for imaging SSTR positive tumors using SPECT, were assessed. Sensitivity of ⁶⁸Ga-DOTATATE and ¹¹¹In-pentetreotide were statistically significantly different (**Table 1**), 96.0% (95% CI: [86.3%; 99.5%]) and 72.0% (95% CI: [57.5%; 83.8%]), respectively, and specificities were similar, 92.9% and 89.3%, respectively. ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate has higher sensitivity than the approved ¹¹¹In-pentetreotide.

Table 1. Sensitivity and Specificity of ⁶⁸Ga-DOTATATE and ¹¹¹In-pentetreotide

⁶⁸ Ga-DOTATATE (n=78)		¹¹¹ In-pentetreotide (n=78)	
Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
96.0 (86.3 99.5)	92.9 (76.5 99.1)	72 (57.7 83.8)	89.3 (71.8 97.7)

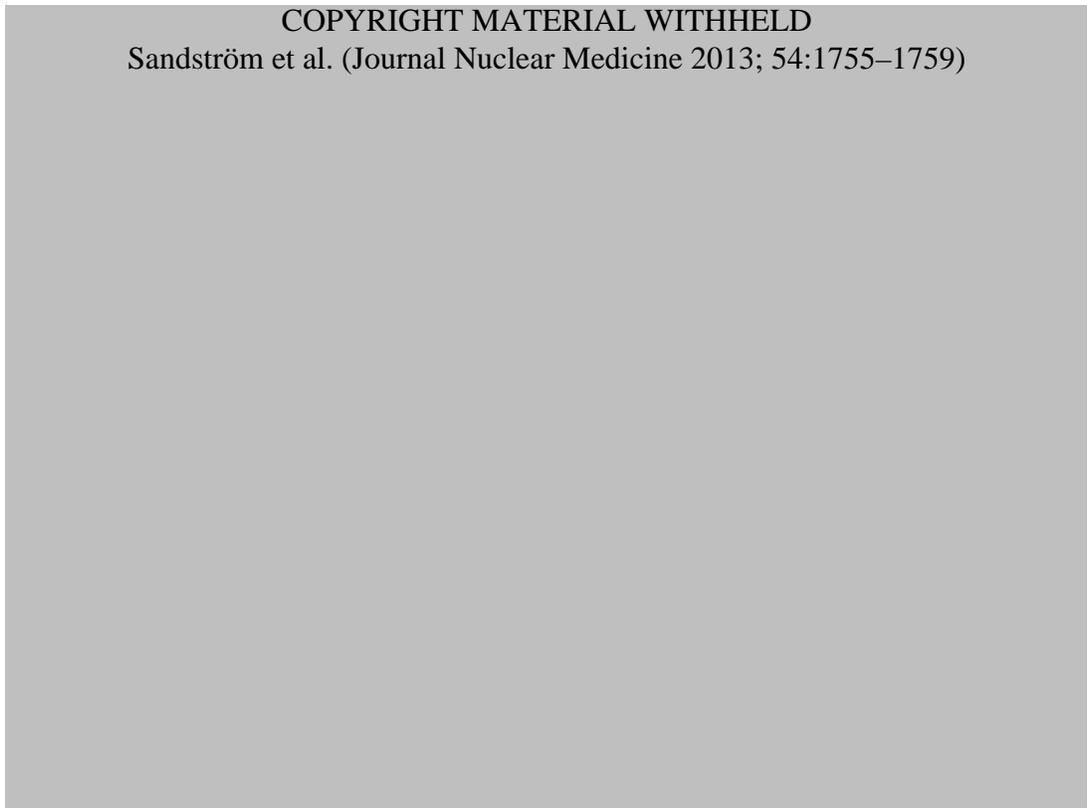
Dose

The earliest trials studied doses ranging from 80 to 200 MBq. The basis for selecting these doses does not appear in the submission or in the literature. No dose finding studies were submitted and none appear in the literature. The proposed package insert dose is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) not more than 200 MBq (5.4 mCi). These doses are consistent with the VUMC trial and literature data. The mass dose of DOTA⁰-Tyr³-Octreotate is approximately 50 ug (a microdose).

Biodistribution

Pharmacokinetics in blood have not been performed. Data on biodistribution is based on imaging. Sandström et al. (Journal Nuclear Medicine 2013; 54:1755–1759) reported biodistribution and dosimetry of ⁶⁸Ga-DOTATATE in nine patients with neuroendocrine tumors after intravenous administration of 91.4±18.7 MBq (range, 72–120 MBq). A 45-min dynamic PET acquisition over the abdominal region, including the liver, spleen, adrenals, and kidneys, was conducted simultaneously with the injection of ⁶⁸Ga-DOTATATE and three whole-body PET acquisitions were performed 1, 2 and 3 hours after injection. Volumes-of-interest (VOIs) were drawn on the whole-body images and on the last time frame of the dynamic image series over “clearly tumor-free” subsets of all clearly identifiable source organs: liver, kidneys, spleen, lungs, small intestine, and adrenal glands. The time-activity curves for major organs taking up ⁶⁸Ga-DOTATATE are shown in **Figure 1**.

Figure 1. Percentage of injected activity (A and B) and SUV (C and D) as a function of time after injection in kidneys, liver, spleen, and red marrow for ^{68}Ga -DOTATATE (A and C) and ^{68}Ga -DOTATOC (B and D). Error bars indicate SEs. SUV data were corrected for radioactive decay; percentage of injected dose data were not.



About 12% of injected radioactivity is excreted in urine in first 4 hours. There is no information on drug biodistribution/PK in patients with hepatic or renal impairment.

Dosimetry

The effective radiation dose (exposure to patients) resulting from the administration of ^{68}Ga -DOTA⁰-Tyr³-Octreotate PET is much lower than that resulting from administration of the approved agent ^{111}In -pentetreotide. The effective radiation dose resulting from the administration of 150 MBq for an adult weighing 75 kg, is about 3.15 mSv as compared to 26 mSv for the 222 MBq dose approved for ^{111}In -pentetreotide.

Intrinsic Factors

There are no data on PK parameters and how they change with intrinsic factors. While pediatric data are not available, a pediatric waiver is not required as ^{68}Ga -DOTA⁰-Tyr³-Octreotate for the current indication has been granted Orphan drug designation.

Extrinsic Factors: Drug-Drug Interactions

Somatostatin analogs are the recommended first line therapy in non-functioning and functioning progressive NETs. Both ^{68}Ga -DOTATATE and “cold” SST analogs bind to SSTR subtype 2. This common molecular target of the medication and the tracer could reduce the specific PET signal by simple competition or by evoking internalization of SSTR2.

To assess the extent of the potential confounding factors, Haug et al. (Treatment with octreotide does not reduce tumor uptake of ^{68}Ga -DOTATATE as measured by PET/CT in patients with neuroendocrine tumors. *J. Nucl Med* 52(11), 1679-1683, 2011) studied the ^{68}Ga -DOTATATE PET standardized uptake values (SUVs) of different tumor sites and healthy organs in groups of patients with or without treatment with “cold” SST analog octreotide at the time of PET. ^{68}Ga -DOTATATE PET/CT was performed in 105 patients, 35 patients had been pretreated with long-acting octreotide and 70 patients were without pre-treatment with SST analogs. The maximum standardized uptake value (SUVmax) of target tissues, as well as metastases, was compared between the groups of patients with (group 1) and without (group 2) octreotide treatment. The SUVmax of the spleen and liver was significantly lower in group 1 than in group 2 (both $p < 0.001$). There were no significant group differences in SUVmax for primary tumors (28.6 ± 6.8 vs. 32.9 ± 31.5) or metastases in the liver (27.2 ± 14.8 vs. 25.7 ± 10.7), lymph nodes (41.4 ± 19.5 vs. 25.0 ± 6.3), or skeleton (39.5 ± 22.0 vs. 15.4 ± 7.8). In 9 patients available for intra-individual comparison, tumor uptake was unaffected by treatment with somatostatin analogs (21.7 vs. 20.6 ; $p = 0.93$). It was concluded that treatment with a long-acting somatostatin analog does not reduce ^{68}Ga -DOTATATE binding in the target tumor in any organ, as opposed to binding in the non-tumorous spleen and liver, where a significant reduction (and thus improved signal-to-background ratio) was observed. This observation advocates the non-interruption of octreotide medication before ^{68}Ga -DOTATATE PET/CT.

While the above data suggest that discontinuing long acting analogs may not be needed, the applicant has proposed discontinuing long acting analogs, and substituting short acting analogs, in order to assure successful imaging. The proposed label states, “*Somatostatin (b)(4) analogs (b)(4) bind to the same somatostatin receptors. (b)(4) long acting analogs of somatostatin (b)(4) Short acting analogs of somatostatin can be used up to 24 hours before (b)(4) imaging (b)(4).*” The reviewer agrees conceptually with the proposed strategy.

SIGNATURES:

Reviewer: Christy S John, Ph.D.
Division of Clinical Pharmacology V

Team Leader: Gene Williams, Ph.D.
Division of Clinical Pharmacology V

Division Director: Nam Atiqur Rahman, Ph.D.
Division of Clinical Pharmacology V

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DCPV: Reviewer C. John; TL G. Williams; DDD B. Booth; DD A. Rahman

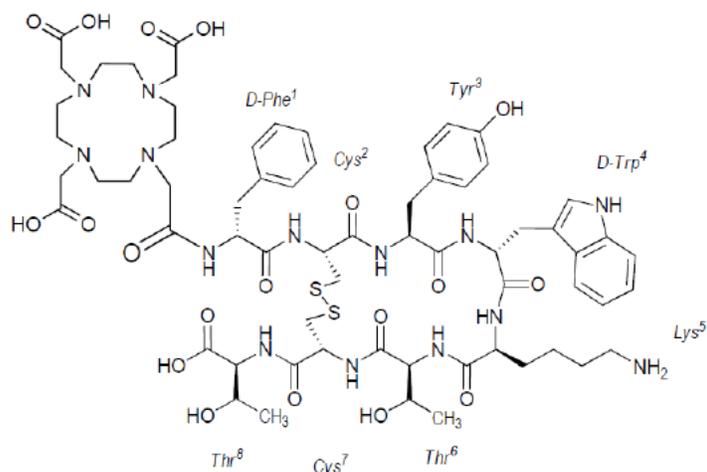
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The kit for preparation of ^{68}Ga -DOTA⁰-Tyr³-Octreotate for injection (drug product) contains the drug substance, DOTA⁰-Tyr³-Octreotate or DOTATATE. DOTA⁰-Tyr³-Octreotate (**Figure 2**) has a molecular weight of 1435.6 Dalton. It is composed of the eight amino acid somatostatin analogue, Tyr³-Octreotate, linked via an amide bond to the metal chelator, DOTA. When the kit is prepared, DOTA is radiolabeled with the 68 min half-life radionuclide Gallium-68, which is a positron emitter.

Figure 2. Structural formula of DOTA⁰-Tyr³-Octreotate



2.1.2 What are the proposed mechanisms of action and therapeutic indications?

The proposed indication is,

(b) (4)

^{68}Ga -DOTA⁰-Tyr³-Octreotate has high affinity for somatostatin subtype 2 receptors (SSTR₂). It binds to cells that express somatostatin receptors including malignant cells, which overexpress sst₂ receptors. Affinity profiles of somatostatin analogues are shown in **Table 2**.

Table 2. Binding affinities [$IC_{50} \pm SEM$, units are nM, number of experiments in parentheses] for SSTR binding drugs

Ligand/SSTR-subtype	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin-28	5.2±0.3 (19)	2.7±0.3 (19)	7.7±0.9 (15)	5.6±0.4 (19)	4.0±0.3 (19)
¹¹¹ In-pentetreotide	>10,000 (6)	22±3.6 (5)	182±13 (5)	>1,000 (5)	237±52 (5)
⁶⁸ Ga-edotreotide	>10,000 (6)	2.5±0.5 (7)	613 ±140 (7)	>1,000 (6)	73±21 (6)
⁶⁸ Ga-DOTATATE	>10,000 (3)	0.2±0.04 (3)	>1,000 (3)	300±140 (3)	377±18 (3)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There are no clinical or clinical pharmacology studies conducted by the applicant. The applicant received data from Vanderbilt University Medical Center (VUMC) for safety and efficacy of ⁶⁸Ga-DOTATATE, and sites additional data from published literature.

The VUMC trial was a prospective, Phase I/II, single center, open-label study. Eligible participants received a one-time administration of ⁶⁸Ga-DOTATATE and underwent a PET/CT imaging study. The one-time nominal injected dose was 5 to 7 mCi in a volume of 3 - 5 ml containing 50 µg ⁶⁸Ga-DOTATATE. Administered activities ranged from 4.3 mCi (159.1 MBq) to 6.0 mCi (222 MBq). However, the vast majority of patients (87.5%) received between 4.9 mCi (181.3MBq) and 5.5 mCi (203.5MBq).

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoints were sensitivity and specificity. The performance of ⁶⁸Ga-DOTATATE PET/CT was compared to that of ¹¹¹In-pentetreotide, an agent approved by FDA for imaging SSTR positive tumors using SPECT, were assessed. Sensitivity of ⁶⁸Ga-DOTATATE and ¹¹¹In-pentetreotide were statistically significantly different (**Table 1**), 96.0% (95% CI: [86.3%; 99.5%]) and 72.0% (95% CI: [57.5%; 83.8%]), respectively, and specificities were similar, 92.9% and 89.3%, respectively.

Table 1. Sensitivity and Specificity of ⁶⁸Ga-DOTATATE and ¹¹¹In-pentetreotide

⁶⁸ Ga-DOTATATE (n=78)		¹¹¹ In-pentetreotide (n=78)	
Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
96.0 (86.3 99.5)	92.9 (76.5 99.1)	72 (57.7 83.8)	89.3 (71.8 97.7)

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

There was no measurement of active moieties in any of the literature articles submitted; no exposure-response relationship was identified.

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

There was no measurement of active moieties in any of the literature articles submitted; no exposure-response relationship was identified.

2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

There was no measurement of active moieties in any of the literature articles submitted; no exposure-response relationship was identified. The drug is used as a micro-dose (approximately 50 ug are administered).

2.2.6 Does this drug prolong the QT or QTc interval?

The mass of ⁶⁸Ga-DOTATATE injected is less than 50 ug. The drug is injected only once, thus the likelihood of QT or QTc prolongation is remote. No QT results are available from the VUMC trial or the literature.

2.2.9 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The earliest trials studied doses of ⁶⁸Ga-DOTATATE ranging from 80-200 MBq. The basis for selecting this dose does not appear in the submission or in the literature. No dose finding studies were submitted and none appear in the literature. The proposed package insert dose is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) not more than 200 MBq (5.4 mCi). In the Vanderbilt study, administered activities ranged from 4.3 mCi (159.1 MBq) to 6.0 mCi (222 MBq). However, the vast majority of patients (87.5%) received between 4.9 mCi (181.3MBq) and 5.5 mCi (203.5MBq). While there is no assurance that an optimal dose has been identified, this is not as unresolved regulatory issue if the proposed microdose is effective.

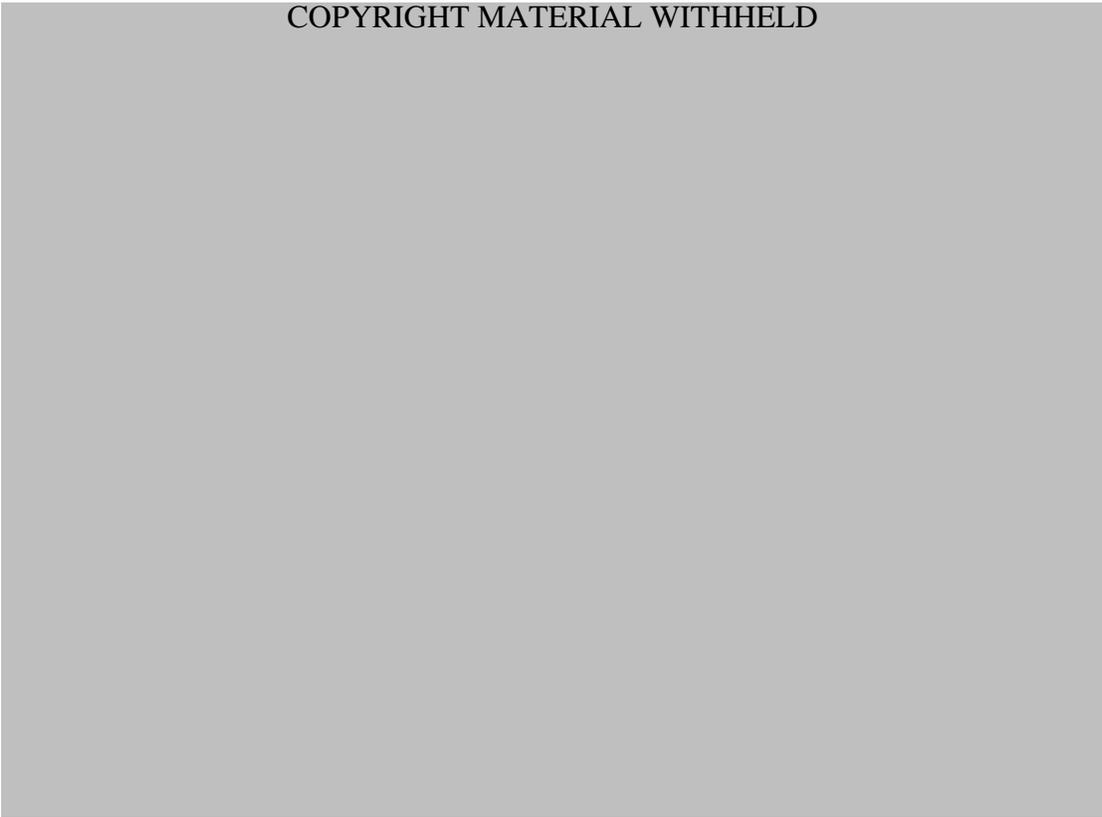
2.2.10 Pharmacokinetic/biodistribution characteristics of the drug and its major metabolites

What are the single dose PK parameters?

Pharmacokinetics in blood have not been performed. Data on biodistribution is based on imaging. Sandström et al. (Journal Nuclear Medicine 2013; 54:1755–1759) reported biodistribution and dosimetry of ^{68}Ga -DOTATATE in nine patients with neuroendocrine tumors after intravenous administration of 91.4 ± 18.7 MBq (range, 72–120 MBq). A 45-min dynamic PET acquisition over the abdominal region, including the liver, spleen, adrenals, and kidneys, was conducted simultaneously with the injection of ^{68}Ga -DOTATATE and three whole-body PET acquisitions were performed 1, 2 and 3 hours after injection. Volumes-of-interest (VOIs) were drawn on the whole-body images and on the last time frame of the dynamic image series over “clearly tumor-free” subsets of all clearly identifiable source organs: liver, kidneys, spleen, lungs, small intestine, and adrenal glands. The time-activity curves for major organs taking up ^{68}Ga -DOTATATE are shown in **Figure 1**.

Figure 1. Percentage of injected activity (A and B) and SUV (C and D) as a function of time after injection in kidneys, liver, spleen, and red marrow for ^{68}Ga -DOTATATE (A and C) and ^{68}Ga -DOTATOC (B and D). Error bars indicate SEs. SUV data were corrected for radioactive decay; percentage of injected dose data were not decay corrected.

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2.2.11 What are the characteristics of drug distribution?

Literature reports using semiquantitative analysis show that, SUVmax values are the highest in the pituitary gland (11 ± 4.5 , mean \pm sd), spleen (18.9 ± 6.6), adrenals (14.0 ± 5.6), and kidneys (14.2 ± 3.6). Significant ^{68}Ga -DOTATATE uptake by the pancreas (SUVmax of 9.2 ± 3.3) was noted in 12% of patients. Moderate ^{68}Ga -DOTATATE uptake was also present in salivary glands (3.4 ± 1.8), thyroid gland (2.9 ± 1.2), and normal liver (6.5 ± 2.2). The bones generally showed low ^{68}Ga -DOTATATE uptake with SUVmax of 1.0 ± 0.3 .

2.2.12 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not reported in submission or in literature.

2.2.13 What are the characteristics of drug metabolism?

^{68}Ga -DOTA⁰-Tyr³-Octreotate's metabolic fate is not known. However, structurally similar analogs do not undergo metabolism and are excreted as parent compounds.

2.2.14 What are the characteristics of drug excretion?

The only available excretion information is a literature report that states that 12% of radioactivity is excreted in urine in the first 4 hours post-administration.

2.2.15 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Data from healthy volunteers were not included in this submission or in the literature.

2.2.16 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

^{68}Ga -DOTATATE is administered only once for imaging purposes in microdose amounts. There is no information available on linearity or non-linearity.

2.2.17 How do the PK parameters change with time following chronic dosing?

^{68}Ga -DOTATATE is given as a microdose and administered only once. There is no information on PK parameters following chronic dosing.

2.2.18 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

There is no information submitted on inter or intra-subject PK variability in healthy subjects or patients.

2.2.19 What is the effective radiation absorbed dose for ⁶⁸Ga-DOTATATE and how does it compare to drugs (111In-pentetreotide) approved for similar indication?

The effective radiation dose (exposure to patients) resulting from the administration of ⁶⁸Ga-DOTA⁰-Tyr³-Octreotate PET is much lower than that resulting from administration of ¹¹¹In-pentetreotide. The effective radiation dose resulting from the administration of 150 MBq for an adult weighing 75 kg, is about 3.15 mSv as compared to 26 mSv for 222 MBq dose approved for ¹¹¹In-pentetreotide for Single Photon Emission Computed Tomography (SPECT) imaging.

2.3 INTRINSIC FACTORS

2.3.1 Do intrinsic factors (race, gender, age, body weight, tumor type, genetic polymorphisms, renal function, and hepatic function) influence the PK of ⁶⁸Ga-DOTATATE and are dose adjustments needed based on these intrinsic factors?

There are no data on PK parameters and how they change with intrinsic factors. ⁶⁸Ga-DOTATATE was used in male and female patients with different types of NETs across all categories of age.

The pediatric assessment is not required for an application to be marketed as a product for an orphan-designated indication. The sponsor states that the product is not indicated for pediatric use because the average presentation of most (b) (4) NETs is greater than 40 years of age.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose adjustments are recommended.

The proposed indication has been granted orphan drug designation. An indication for pediatric use has not been proposed by the applicant. No data on pediatric imaging is present in the submission or in the literature.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, diet, and alcohol use on the dose-exposure and/or dose-response for ⁶⁸Ga-DOTATATE have not been assessed. The drug is administered intravenously, exclusively.

Drug-drug interactions

2.4.2 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

2.4.3 Is the drug a substrate of CYP enzymes?

⁶⁸Ga-DOTATATE is a peptide with 8 amino acids with a covalently bound chelator. It is not expected to be metabolized by CYP enzymes. There are no *in vitro* data available.

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes?

2.4.6 Are other metabolic/transporter pathways important?

⁶⁸Ga-DOTATATE is a peptide with 8 amino acids with a covalently bound chelator. It is not known if the drug is a substrate of CYP enzyme. The drug is administered as a microdose (approximately 50 ug). It is unlikely to act as a significant inhibitor or inducer at the concentrations resulting from the microdose.

2.4.7 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Somatostatin analogs are the recommended first line therapy in non-functioning and functioning progressive NETs. Both ⁶⁸Ga-DOTATATE and “cold” SST analogs bind to SSTR subtype 2. This common molecular target of the medication and the tracer could reduce the specific PET signal by simple competition or by evoking internalization of SSTR2.

To assess the extent of the potential confounding factors, Haug et al. (Treatment with octreotide does not reduce tumor uptake of ⁶⁸Ga-DOTATATE as measured by PET/CT in patients with neuroendocrine tumors. J. Nucl Med 52(11), 1679-1683, 2011) studied the ⁶⁸Ga-DOTATATE PET standardized uptake values (SUVs) of different tumor sites and healthy organs in groups of patients with or without treatment with “cold” SST analog octreotide at the time of PET. ⁶⁸Ga-DOTATATE PET/CT was performed in 105 patients, 35 patients had been pretreated with long-acting octreotide and 70 patients were without pre-treatment with SST analogs. The maximum standardized uptake value (SUV_{max}) of target tissues, as well as metastases, was compared between the groups of patients with (group 1) and without (group 2) octreotide treatment. The SUV_{max} of the spleen and liver was significantly lower in group 1 than in group 2 (both $p < 0.001$). There were no significant group differences in SUV_{max} for primary tumors (28.6 ± 6.8 vs. 32.9 ± 31.5) or metastases in the liver (27.2 ± 14.8 vs. 25.7 ± 10.7), lymph nodes (41.4 ± 19.5 vs. 25.0 ± 6.3), or skeleton (39.5 ± 22.0 vs. 15.4 ± 7.8). In 9 patients available for intra-individual comparison, tumor uptake was unaffected by treatment with somatostatin analogs (21.7 vs. 20.6 ; $p = 0.93$). It was concluded that treatment with a long-acting somatostatin analog does not reduce ⁶⁸Ga-DOTATATE binding in the target tumor in any organ, as opposed to binding in the non-tumorous spleen and liver, where a significant reduction (and thus improved signal-to-background ratio) was observed. This observation advocates the non-interruption of octreotide medication before ⁶⁸Ga-DOTATATE PET/CT.

While the above data suggest that discontinuing long acting analogs may not be needed, the applicant has proposed discontinuing long acting analogs, and substituting short acting analogs,

in order to assure successful imaging. The proposed label states, “Somatostatin (b) (4) analogs (b) (4) bind to the same somatostatin receptors. (b) (4) long acting (b) (4) analogs of somatostatin (b) (4) Short acting analogs of somatostatin can be used up to 24 hours before (b) (4) imaging (b) (4).” The reviewer agrees conceptually with the proposed strategy. Final package insert language is addressed in section 3 Detailed Labeling Recommendations of this review.

2.4.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No, see 2.4.7, above

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.5.2 What is the composition of the to-be-marketed formulation?

2.5.3 What moieties should be assessed in bioequivalence studies?

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

BCS classification and bioavailability are not issues for this parenteral formulation.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

2.6.2 Which metabolites have been selected for analysis and why?

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>)

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

There are no available data submitted in the application or in the literature on parent or metabolite concentration measurement.

3 DETAILED LABELING RECOMMENDATIONS

Clinical pharmacology related sections of the applicant's proposed package insert, together with FDA's most current revisions (as tracked changes), begin on the following page of this review. FDA's edits may undergo further revision, as they have not been conveyed to and negotiated with the applicant.

APPLICANT'S PROPOSED	RECOMMENDED BY REVIEWER
<p>7 DRUG INTERACTIONS</p> <p>7.1 Somatostatin Analogs</p> <p>Non-radioactive somatostatin analogs competitively bind to the same somatostatin receptor (b) (4) long acting analogs of somatostatin (b) (4)</p> <p>Short acting analogs of somatostatin can be used up to 24 hours before (b) (4) imaging (b) (4).</p>	<p>7 DRUG INTERACTIONS</p> <p>7.1 Somatostatin Analogs</p> <p>Non-radioactive somatostatin analogs competitively bind to the same somatostatin receptors. (b) (4) long acting analogs of somatostatin (b) (4)</p> <p>Short acting analogs of somatostatin can be used up to 24 hours before (b) (4) imaging (b) (4).</p>
(b) (4)	
<p>(b) (4)</p> <p>(b) (4) It binds to cells that express somatostatin receptors including malignant cells, which overexpress sst₂ receptors.</p> <p>Gallium-68 (⁶⁸Ga) is a β⁺ emitting radionuclide with (b) (4) emission yield (b) (4) that (b) (4) positron emission tomography (PET) imaging.</p> <p>12.2 Pharmacodynamics</p>	<p>12.1 Mechanism of Action</p> <p>(b) (4) It binds to cells that express somatostatin receptors including malignant cells, which overexpress sst₂ receptors.</p> <p>Gallium-68 (⁶⁸Ga) is a β⁺ emitting radionuclide with (b) (4) emission yield. (b) (4) that (b) (4) positron emission tomography (PET) imaging.</p> <p>12.2 Pharmacodynamics</p>
(b) (4)	

12.3 Pharmacokinetics

Distribution

(b) (4)

$^{68}\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ distributes (b) (4) all sstr2-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate liver, salivary glands (b) (4). There is no uptake in the cerebral cortex or in the heart, and usually thymus and lung uptakes are low

(b) (4)

(b) (4) elimination

(b) (4)

12.3 Pharmacokinetics

Distribution

(b) (4)

$\text{Ga-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ distributes (b) (4) all sstr2-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate liver, salivary glands (b) (4). There is no uptake in the cerebral cortex or in the heart, and usually thymus and lung uptakes are low

(b) (4)

(b) (4) **Metabolism** and elimination (b) (4)

(b) (4)

(b) (4)

4 APPENDICES

4.1 OCP FILING FORM

APPEARS THIS WAY ON ORIGINAL

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology			
<i>New Drug Application Filing and Review Form</i>			
<u>General Information About the Submission</u>			
	Information		Information
NDA/BLA Number	208547	Brand Name	(b) (4) ®: Kit for preparation of 68GA-DOTA0-Tyr3-Octreotate for injection
OCP Division (I, II, III, IV, V)	V	Generic Name	Kit for preparation of 68GA-DOTA0-Tyr3-Octreotate for injection
Medical Division	DMIP	Drug Class	Imaging
OCP Reviewer	Christy S John, Ph.D.	Indication(s)	⁶⁸ Ga-DOTA ⁰ -Tyr ³ -Octreotate is a radioactive diagnostic agent indicated (b) (4) (b) (4)

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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OCP Team Leader	Gene Williams, Ph.D.	Dosage Form	(b) (4) is supplied as a mono dose kit containing: One vial of lyophilizate containing 40µg of DOTA ⁰ -Tyr ³ -Octreotate; One vial of 1 ml of reaction buffer solution; One accessory cartridge	
Pharmacometrics Reviewer	N/A	Dosing Regimen	For PET imaging (b) (4) The recommended radioactivity to be administered is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) not more than 200 MBq (5.4 mCi).	
Date of Submission	July 1, 2015	Route of Administration	IV Injection	
Estimated Due Date of OCP Review	October 16, 2015	Sponsor	Advanced Accelerator Applications, USA Inc.	
Medical Division Due Date	November 8, 2015	Priority Classification	P	
PDUFA Due Date	January 1, 2016			
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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STUDY TYPE				This application is supported by literature references. Studies relating to ⁶⁸ Ga-DOTATATE efficacy and mechanism of action accounted for 26 publications. Studies relating to ⁶⁸ Ga-DOTATATE safety accounted for 8 publications. The clinical pharmacology is supported by 10 publications.
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Drug-drug interaction studies				
-				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	X			
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Literature References	X	10		
Total Number of Studies	10	10		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X		X	
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?		X		Applicant has used literature data to support PK
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?			

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____X_____

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Christy S John, Ph.D.

Reviewing Clinical Pharmacologist

Date

Gene Williams, Ph.D.

Team Leader/Supervisor

Date

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
09/08/2015

GENE M WILLIAMS
09/08/2015

I concur with the recommendations.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
12/03/2015

GENE M WILLIAMS
12/03/2015
I concur with the recommendations

NAM ATIQR RAHMAN
12/03/2015
I concur with the team's recommendation.