CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208054Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
NDA	208-547
Submission Date	September 28, 2015 (SDN 2) December 4, 2015 (SDN 8) January 20, 2016 (SDN 16)
Brand Name	Auxumin {*anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid; [^{18}F-Fluciclovine]}
Formulation	Solution for Injection
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	Blue Earth Diagnostics, Ltd.
Submission Type; Code	Original-1 (Type 1- New Molecular Entity)
Dosing regimen	The recommended activity for an adult is 370 MBq (10 mCi) administered as a (b) (4) intravenous injection. The recommended maximum volume of injection of undiluted Axumin is 5mL.
Indication	Axumin is a radioactive diagnostic agent for positron emission tomography (PET) imaging (b) (4) men with suspected prostate cancer recurrence. (b) (4) based (b) (4) on elevated blood prostate specific antigen (PSA) levels following (b) (4)

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1 EXECUTIVE SUMMARY

Blue Earth Diagnostics has submitted NDA 208-054 for Axumin "for positron emission tomography (PET) imaging (b)(4) men with suspected prostate cancer recurrence. (b)(4) Suspected prostate cancer recurrence is based (b)(4) on elevated blood prostate specific antigen (PSA) levels following (b)(4) The application relies on data from clinical trials reported in the literature.

Axumin's active ingredient is ^{18}F-Fluciclovine, a synthetic L-leucine analogue which is actively transported into mammalian cells by amino acid transporters (AAT). The principle transporters involved in the uptake of ^{18}F-Fluciclovine are LAT1 and ASC2, which have been shown to be up-regulated in many cancer cells.

A prospective, comparative study of the diagnostic performance of ^{18}F-Fluciclovine and the approved drug ProstaScint (^{111}In-Capromab pendetide, used for SPECT imaging) in the detection of recurrent prostate cancer was conducted by a primary investigator at Emory University. The clinical endpoints were sensitivity and positive predictive value (PPV). In the prostate/bed at the lesion level, using biopsy findings as standard-of-truth (SOT), ^{18}F-Fluciclovine had a sensitivity of 90.2% (95% CI 79.8 - 96.3) compared to 67.2% (95% CI 54.0 - 78.7) for ProstaScint. Outside the prostate/bed, ^{18}F-Fluciclovine had a sensitivity of 55% (95% CI 38.5 - 70.7) compared to 10% (95% CI 2.8 - 23.7) for ProstaScint. The PPVs for ^{18}F-Fluciclovine and ProstaScint were about the same for both drugs at 75.3 % and 75.9 %, respectively. The PPV for the extra-prostatic region was much higher for ^{18}F-Fluciclovine (95.7%) than for ProstaScint (50.0 %).

^{18}F-Fluciclovine is administered as a microdose ($\leq$ 10 ug). Clinical trials studied radioactive doses ranging from 162 to 484 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, although there is literature report that doses of 200 MBq were ineffective. The proposed dose is 370 MBq (10 mCi).

The effective radiation dose (exposure to patients) resulting from the administration of ^{18}F-Fluciclovine is less than one third of that resulting from administration of ProstaScint. The effective radiation dose resulting from the administration of 370 MBq for an adult weighing 75 kg, is about 8.2 mSv as compared to 27 mSv for the 185 MBq dose approved for ProstaScint.

The pharmacokinetics of ^{18}F-Fluciclovine were not assessed, and elimination was not well characterized. Over 24 hours, 5.4% of administered radioactivity was excreted in urine.

No drug interaction studies were conducted by the applicant or reported in the literature. Because only a single microdose is administered, fluciclovine is unlikely to perpetrate drug interactions. Only trace amounts of metabolites were present in plasma and urine samples, making it unlikely that fluciclovine would be a victim of metabolic drug interactions.

1.1 Recommendations

The efficacy and safety of Axumin is based on a comparative clinical study that established the diagnostic performance of ^{18}F-Fluciclovine in the detection of the recurrent prostate cancer. The drug is given as a single microdose that provides lower radiation exposure than the product currently marketed for a similar indication. The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 208-054 and recommends approval of the application.

Drug Development Decision	**Sufficiently Supported?**	**Recommendations and Comments**
Overall	☑Yes ☐No	
Evidence of effectiveness	☑Yes ☐No Refer to Section 2.2.2	Based on a comparative study conducted by an investigator at Emory University (Study R01)
Proposed dose for general population	☑Yes ☐No Refer to Section 2.2.9	10 mCi by intravenous injection.
Proposed dose selection for others	☑Yes ☐No Refer to Section 2.2.9	Single microdose administration
Labeling	☑Yes ☐No Refer to Section 3.0	Minor edits

Labeling Recommendations

Refer to Section **3 DETAILED LABELING RECOMMENDATIONS**.

1.2 Post-Marketing Requirements and Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Blue Earth Diagnostics has submitted NDA 208-054 for Axumin "for positron emission tomography (PET) imaging (b)(4) men with suspected prostate cancer recurrence. (b)(4) Suspected prostate cancer recurrence is based (b)(4) on elevated blood prostate specific antigen (PSA) levels following (b)(4) This application relies on clinical trials from the literature.

Axumin contains ^{18}F-Fluciclovine (**Figure 1**) is a synthetic L-leucine analogue which is actively transported into mammalian cells by amino acid transporters (AAT). The principle transporters involved in the uptake of ^{18}F-Fluciclovine are LAT1 and ASC2, which have been shown to be upregulated in cancer cells.

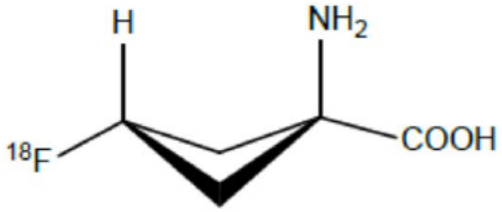

Figure 1. Chemical structure of ^{18}F-Fluciclovine

Efficacy

A prospective, comparative study of the diagnostic performance of ^{18}F-Fluciclovine and the approved drug ProstaScint (^{111}In-Capromab pendetide, used for SPECT imaging) in the detection of recurrent prostate cancer was conducted by a primary investigator at Emory University. The clinical endpoints were sensitivity and positive predictive value (PPV). Results are shown in **Table 1**. In the prostate/bed at the lesion level, using biopsy findings as standard-of-truth (SOT), ^{18}F-Fluciclovine had a sensitivity of 90.2% (95% CI 79.8 - 96.3) compared to 67.2% (95% CI 54.0 - 78.7) for ProstaScint. Outside the prostste/bed, ^{18}F-Fluciclovine had a sensitivity of 55% (95% CI 38.5 - 70.7) compared to 10% (95% CI 2.8 - 23.7) for ProstaScint. Positive predictive values (PPV) for ^{18}F-Fluciclovine and ProstaScint were about the same for both drugs at 75.3 % and 75.9 %, respectively. PPV for the extra-prostatic region was much higher for ^{18}F-Fluciclovine (95.7%) than for ProstaScint (50.0 %).

Table 1*. Anti-3-[^{18}F]FACBC (^{18}F-Fluciclovine) vs ^{111}In-capromab pendetide diagnostic performance in prostate/bed and extraprostatic sites

	Anti-3-[^{18}F]FACBC	^{111}In-Capromab Pendetide	p Value
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*Results taken from a publication by the primary investigator at Emory (M. Schuster et al. Anti-3-[^{18}F]FACBC Positron Emission Tomography-Computerized Tomography and ^{111}In-Capromab Pendetide Single Photon Emission Computerized Tomography-Computerized Tomography for Recurrent Prostate Carcinoma: Results of a Prospective Clinical Trial. J. Urology 2014, 1446-1453).

Dose

Clinical trials from various institutions (Oslo University, Bologna University, Emory University and Aleris, Norway) studied doses of ^{18}F-Fluciclovine varying from 162 - 485 MBq (4.4 to 13.1 mCi). The investigators from Oslo University used a dose of 200 MBq and concluded that ineffective images were obtained. The basis for selecting doses does not appear in the submission or in the literature. No dose finding studies appeared in the literature or were conducted by the applicant. The proposed package insert recommends a dose of 370 MBq or 10 mCi by intravenous injection in a total volume not exceeding 5 mL. The mass dose of ^{18}F-Fluciclovine is 2 ug/mL (max of 10 ug).

In Emory study (primary efficacy study) the mean (median) dose administered in patients with a positive scan finding (n=90) is 357.7MBq; 9.7mCi (370MBq;10mCi) while in those with negative findings on the fluciclovine PET-CTscan (n=14) the mean(median) dose administered is 361.8MBq [9.8Ci] (362.6 MBq;9.8mCi) respectively.

Biodistribution

Assessment of ^{18}F activity in healthy subjects showed the distribution to be mostly uniform throughout the body with the exceptions of the brain, red bone marrow, liver, and pancreas. There was very little brain uptake (1.6%). The 4 organs with the highest initial uptake of ^{18}F were the liver (13.8%), red bone marrow (11.1%), lung (7.1%), and pancreas (4.2%). The critical organ (i.e., that with the highest absorbed dose per unit administered activity) was the pancreas, with a mean absorbed dose of 103 microGy/MBq.

Dosimetry

The effective radiation dose (exposure to patients) resulting from the administration of ^{18}F-Fluciclovine is much lower than that resulting from administration of Prostascint. The effective radiation dose resulting from the administration of 370 MBq for an adult weighing 75 kg is about 8.2 mSv as compared to 27 mGy (27 mSv) for the 185 MBq dose approved for Prostacint.

Intrinsic Factors

Pharmacokinetics were not performed. While pediatric data are not available, a pediatric waiver was granted as prostate cancer is a disease of adult males (b) (4).

Extrinsic Factors

Drug interaction studies have not been performed. Because only a single microdose is administered, fluciclovine is unlikely to perpetrate drug interactions. Only trace amounts of metabolites were present in plasma and urine samples, making it unlikely that fluciclovine would be a victim of metabolic drug interactions.

SIGNATURES

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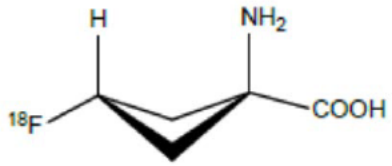
2 QUESTION BASED REVIEW

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?

Axumin contains ^{18}F-Fluciclovine, a synthetic amino acid analog for PET imaging to visualize increased amino acid transport that occurs in malignant tumors. Chemically, ^{18}F-Fluciclovine is described as ^{18}F labeled *anti*-1-amino-3-fluorocyclobutane-1-carboxylic acid. The molecular weight is 132.1 and the structural formula is shown in Figure 1.

Figure 1. Chemical structure of [^{18}F-Fluciclovine]



Axumin is a sterile, non-pyrogenic, clear, colorless solution for intravenous injection. Each milliliter of solution contains up to (b) (4) micrograms of fluciclovine and 335 to 8200 MBq (9 to 221 mCi) ^{18}F-Fluciclovine at calibration time and date, (b) (4) trisodium citrate (b) (4) hydrochloric acid and (b) (4) sodium hydroxide (b) (4). The pH of the solution is between (b) (4) and 6.0. ^{18}F-Fluciclovine solution for injection is presented in a multi-dose vial of capacity 30 mL containing approximately 26 mL of product. The maximum recommended injection volume of undiluted product is 5 mL. The mass content of fluciclovine is not more than 2 µg/mL.

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

^{18}F-Fluciclovine is a synthetic L-leucine analogue which is actively transported into mammalian cells by amino acid transporters (AAT). The principle transporters involved in the uptake of ^{18}F-Fluciclovine are LAT1 and ASC2, which have been shown to be upregulated in cancer cells.

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. No dose finding studies were conducted by the applicant or in any published literature. The applicant received data from Emory University (Study RO1) for safety and efficacy of ^{18}F-Fluciclovine, and cites additional data from published literature. Biodistribution data was received from GE Healthcare and (b) (4).

A prospective, comparative study of the diagnostic performance of ^{18}F-Fluciclovine and the approved drug ProstaScint (^{111}In-Capromab pendetide, used for SPECT imaging) in the detection of recurrent prostate cancer was conducted by a primary investigator at Emory University. This study enrolled patients with suspected recurrent disease (defined either by ASTRO criteria (3 consecutive PSA increases) and/or ASTRO/Phoenix criteria (nadir PSA greater than 2.0 ng/ml after radiotherapy or cryotherapy and/or greater than 0.2 ng/ml after prostatectomy) after definitive treatment for local prostate cancer, and evaluated the performance of ^{18}F-Fluciclovine in both the prostate or prostate bed and extraprostatic sites.

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 positive predictive value (PPV). Results are shown in **Table 1**. In the prostate/bed at the lesion level, using biopsy findings as standard-of-truth (SOT), ^{18}F-Fluciclovine had a sensitivity of 90.2% (95% CI 79.8 96.3) as compared to 67.2% (95% CI 54.0 78.7) for ProstaScint. Outside the prostate/bed, ^{18}F-Fluciclovine had a sensitivity of 55% (95% CI 38.5 70.7) compared to 10% (95% CI 2.8 23.7) for ProstaScint. Positive predictive values (PPV) for ^{18}F-Fluciclovine and ProstaScint were about the same for both drugs at 75.3 % and 75.9 %, respectively. PPV for extraprostatic region was much higher for ^{18}F-Fluciclovine (95.7%) than for ProstaScint (50.0%).

Table 1*. Anti-3-[^{18}F]FACBC (^{18}F-Fluciclovine) vs ^{111}In-capromab pendetide diagnostic performance in prostate/bed and extraprostatic sites

	Anti-3-[^{18}F]FACBC	^{111}In-Capromab Pendetide	p Value
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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 studies on imaging performance.

Pharmacokinetic studies quantitated only parent drug. The main impurity present in the formulation intended for marketing, (b) (4) has a similar uptake profile to fluciclovine, although its affinity for AATs is much lower than that of fluciclovine. It is similarly not incorporated in to newly synthesized proteins. (b) (4) is unlikely to have any impact on the uptake of fluciclovine at the clinical dose. The maximum chemical concentrations of fluciclovine and (b) (4) in the drug product are (b) (4) respectively. Based on the maximum recommended dose volume of 5mL, this is equivalent to maximum concentrations in plasma (assuming a 5 L blood volume) of (b) (4) respectively, which are orders of magnitude lower than the concentrations at which the in vitro uptake of fluciclovine is saturated ((b) (4)) or inhibited by (b) (4) (IC_{50} of (b) (4)).

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

Pharmacokinetics have not been performed.

Dose-response analyses were not conducted by the applicant. Using data from the Emory study, the only study for which data allowing dose-response analysis are available, the reviewer analyzed sensitivity, which is the endpoint of greatest value for the indication. Results are presented in **Table 2**. No dose-response relationship is observed.

Table 2. Imaging outcome and radioactivity doses

	N = number of scans	Mean dose (MBq)	St dev dose (MBq)
scans with lesions not detected by ^{18}F-Fluciclovine	5	376	17
scans with lesions detected by ^{18}F-Fluciclovine	75	355	54

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

Pharmacokinetics have not been performed. The drug is used as a micro-dose (approximately 10 ug is administered).

2.2.6 Does this drug prolong the QT or QTc interval?

The mass of ^{18}F-Fluciclovine injected is about 10 ug. The drug is injected only once, thus the likelihood of QT or QTc prolongation is remote. There were no significant effects of ^{18}F-Fluciclovine injection on ECG interval changes in mean values or shifts from baseline in ECG parameters. There were no ECG abnormalities or trends indicative of a safety signal detected in subjects with prostate cancer or HV s. There were no clinically significant or non-clinically significant ECG findings or QTc intervals >500 msec at any time point during the study.

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?

Clinical trials from various institutions (Oslo University, Bologna University, Emory University and Aleris, Norway) studied doses of ^{18}F-Fluciclovine varying from 162 - 485 MBq (4.4 to 13.1 mCi). The investigators from Oslo University used a dose of 200 MBq and concluded that ineffective images were obtained. The basis for selecting doses does not appear in the submission or in the literature. No dose finding studies appeared in the literature or were conducted by the applicant. The proposed package insert recommends a dose of 370 MBq or 10 mCi by intravenous injection in a total volume not exceeding 5 mL. The mass dose of ^{18}F-Fluciclovine is 2 ug/mL (max of 10 ug). While there is no assurance that an optimal dose has been identified, this is not an unresolved regulatory issue if the proposed dose is effective.

2.2.10 What are the single dose PK parameters?

Pharmacokinetics have not been performed. In Study GE148-001 blood samples were taken with the intention of determining the percentage of the total activity present as the parent compound over time. However, the applicant states that it was not possible to develop methods to detect ^{18}F-Fluciclovine in the blood.

2.2.11 What are the characteristics of drug distribution?

Assessment of ^{18}F activity in healthy subjects showed the distribution to be mostly uniform throughout the body with the exceptions of the brain, red bone marrow, liver, and pancreas. There was very little brain uptake (1.6%). The 4 organs with the highest initial uptake of ^{18}F were the liver (13.8%), red bone marrow (11.1%), lung (7.1%), and pancreas (4.2%). The critical organ (i.e., that with the highest absorbed dose per unit administered activity) was the pancreas, with a mean absorbed dose of 103 microGy/MBq.

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 the submission or in literature.

2.2.13 What are the characteristics of drug metabolism?

^{18}F-Fluciclovine does not undergo significant metabolism. Plasma radioluminography (RLG) detected only one peak with an Rf value consistent with that of *anti*-FACBC standard product (Rf = 0.25–0.29) at all blood sampling time points. Urine RLG also detected a peak with an Rf value consistent with that of *anti*-FACBC parent as the main component, suggesting that the radioactivity in plasma and urine was predominantly in the form of unmetabolized drug. Although urine RLG also detected two other unidentified peaks, the mean dose equivalents of those peaks were 0.00500 %ID (Rf = 0.00) and 0.0717 %ID (Rf = 0.20–0.24). Two unidentified peaks were detected in Study NMK36-P1, however, the dose equivalents for these peaks were 0.005 %ID and 0.0717 %ID indicating that they were present in negligible amounts.

2.2.14 What are the characteristics of drug excretion?

The excretion of ^{18}F-Fluciclovine in humans has not been well characterized. In Study GE-148-001, a mean of 3.2 % of activity was excreted in the urine in over the collection period (mean 4.2 hours). Study NMK36-P1 collected for 24 hours, over which time a mean of 5.4% of activity was excreted in the urine.

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

Pharmacokinetics have not been performed.

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

Pharmacokinetics have not been performed. ^{18}F-Fluciclovine is administered only once and in a microdose amount.

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

Pharmacokinetics have not been performed. ^{18}F-Fluciclovine is administered only once and as in a microdose amount.

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?

Pharmacokinetics have not been performed.

2.2.19 What is the effective radiation absorbed dose for ^{18}F-Fluciclovine and how does it compare to drugs (^{111}In-cabromab pendetide (Prostascint)) approved for similar indications?

The effective radiation dose (exposure to patients) resulting from the administration of ^{18}F-Fluciclovine PET is much lower than that resulting from administration of Prostacint. The effective radiation dose resulting from the administration of 370 MBq for an adult weighing 75

kg is about 6.3 mSv as compared to 27 mGy (27 mSv) for the 185 MBq dose approved for Prostacint.

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 and are dose adjustments needed based on these intrinsic factors?

Pharmacokinetics have not been performed.

A pediatric waiver was granted to the applicant as prostate cancer is predominantly an adult male [redacted] (b) (4) disease.

Sub-group analyses revealed that there was no obvious impact of age, race, prior cancer treatment, and Gleason score or D'Amico risk score of the primary tumor on ^{18}F-Fluciclovine PET-CT scan performance. With respect to the impact of PSA value on ^{18}F-Fluciclovine PET-CT scan performance, there was generally a lower detection rate (DR) in subjects in the first quartile of PSA values (PSA ≤0.79 ng/mL) at the lesion level. At the region level ^{18}F-Fluciclovine PET-CT scan performance in the Prostate/Prostate bed was similar in these subjects to those with higher PSA values at the time of scanning and as a consequence, the assessment of ^{18}F-Fluciclovine PET-CT performance at the subject level was similar regardless of the PSA value at baseline.

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.

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?

Effects of extrinsic factors such as herbal products, diet, and alcohol have not been assessed. Although the drug is administered exclusively intravenously, there is a theoretical possibility of a food effect as the drug is transported by amino acid transporters. This is discussed in section **2.5.4.**

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?

There is no evidence of any significant metabolism of ^{18}F-Fluciclovine in any of the *in vitro*, *in vivo* or published studies. Unidentified peaks have been detected (see section **2.2.13**), however, the dose equivalents for these peaks indicate that the moieties were present in negligible amounts.

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

Fluciclovine has not been studied as a CYP inhibitor or inducer. It is administered in microdose amounts: the potential for it to perpetrate drug interactions is remote.

2.4.5 Is the drug a substrate of P-glycoprotein (P-gp) transport processes?

At concentrations up to 10 μM, fluciclovine was not a substrate for OAT1, OATP1B1, OAT3 and OCT2.

Fluciclovine exhibits concentration-dependent inhibition of BCRP, MDR1 and MRP4. However, IC_{50} values were > 1 mM. While Cmax is unknown, 1 mM is 40000-fold greater than dose/plasma volume (a "worst case" over-estimate of maximal concentration). No effect of ^{18}F-Fluciclovine on transporters is expected.

2.4.6 Are other metabolic/transporter pathways important?

There are no known "other pathways" for fluciclovine. 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?

The label does not specify co-administration of another drug.

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 in vivo drug interaction studies were performed.

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?

Because fluciclovine is an amino acid, the reviewer considered whether a high protein meal might alter distribution. Ingestion of a high protein meal elevates plasma amino acid levels by ~25% during the first 1-2 hours following the meal, with levels returning to pre-prandial levels after 4-8 hours (E. Nasset et al. J. Nutrition 109, 621-630, 1979). It is very unlikely that the a 25% increase in total circulating amino acids would have any significant effect on transport and resulting image quality.

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?

Pharmacokinetics have not been performed.

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 (**Table 3.**) of this review. FDA's edits may undergo further revision, as they have not been conveyed to and negotiated with the applicant.

Table 3. Package Insert

APPLICANT'S PROPOSED	RECOMMENDED BY REVIEWER
(b) (4)	
8 USE IN SPECIFIC POPULATIONS **8.4 Pediatric Use** (b) (4) safety and effectiveness (b) (4) have not been established in pediatric patients.	**8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** (b) (4) safety and effectiveness (b) (4) have not been established in pediatric patients.
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of action** Fluciclovine F 18 is a synthetic amino acid (b) (4) transported across mammalian cell membranes by amino acid transporters, such as LAT-1 and ASCT2 which are (b) (4) upregulated in (b) (4) cance (b) (4)	**12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of action** Fluciclovine F 18 is a synthetic amino acid (b) (4) transported across mammalian cell membranes by amino acid transporters, such as LAT-1 and ASCT2 which are (b) (4) upregulated in (b) (4) cancer (b) (4)
12.2 Pharmacodynamics (b) (4)	**12.2 Pharmacodynamics** (b) (4)
12.3 Pharmacokinetics *Distribution*: (b) (4)	**12.3 Pharmacokinetics** *Distribution*: (b) (4) (b) (4)


(b) (4)

4 APPENDICES

4.1 Applicant’s Proposed Package Insert

4.2 OCP Filing Form

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

4.2 OCP Filing Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208-054	**SDN**	2
Applicant	Blue Earth Diagnostics Ltd.	**Submission Date**	9/28/2015
Generic Name	Fluciclovine F 18 (proposed USAN)	**Brand Name**	AXUMIN
Drug Class	PET Imaging agent		
Indication	Axumin is a radioactive diagnostic agent for positron emission tomography (PET) imaging (b) (4) men with suspected prostate cancer recurrence. (b) (4) based (b) (4) on elevated blood prostate specific antigen (PSA) levels following (b) (4)		
Dosage Regimen	10 mCi (370 MBq) as a (b) (4) intravenous injection		
Dosage Form	Axumin is supplied in 30 mL multi dose vials containing a colorless injectable solution at a strength of 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F18 at calibration time and date	**Route of Administration**	IV push
OCP Division		**OND Division**	

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Christy S John, Ph.D.	Gene Williams, Ph.D.
Pharmacometrics	N/A	N/A
Genomics	N/A	N/A

Review Classification	☐ Standard ☐ Priority ☐ Expedited		
Filing Date	10/28/2015	**74-Day Letter Date**	11/17/2015
Review Due Date	2/19/2016	**PDUFA Goal Date**	5/27/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☐ No

If yes list comment(s)

Please provide the bioanalytical method reports, including raw concentration-time data, for the PK data in the submission. Also provide the corresponding assay method validation reports.

Please provide in electronic format (.xpt) patient level dosing data for all the clinical studies including the Emory and Bologna studies. The provided data will be merged with previously submitted datasets, so each

patient needs a unique identifier that will allow such merging.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☐ Yes ☑ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☑ Metabolism Characterization		1	
☑ Transporter Characterization		3	
☐ Distribution			
☑ Drug-Drug Interaction		1	
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability		N/A	
☐ Relative Bioavailability		N/A	
☐ Bioequivalence		N/A	
☐ Food Effect		N/A	
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	2	
	☐ Multiple Dose	N/A	
Patients	☑ Single Dose	2	
	☐ Multiple Dose		
☐ Mass Balance Study		0	
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race		0	
☐ Sex		N/A	
☐ Geriatrics		0	
☐ Pediatrics		N/A	
☐ Hepatic Impairment		0	
☐ Renal Impairment		0	
☐ Genetics		0	
Extrinsic Factors			

☐ Effects on Primary Drug	0			
☐ Effects of Primary Drug	0			
Pharmacodynamics				
☐ Healthy Subjects				
☐ Patients				
Pharmacokinetics/Pharmacodynamics				
☐ Healthy Subjects	1			
☐ Patients	1			
☐ QT				
Pharmacometrics				
☐ Population Pharmacokinetics	0			
☐ Exposure-Efficacy	0			
☐ Exposure-Safety	0			
Total Number of Studies		**In Vitro**	4	**In Vivo** 5
Total Number of Studies to be Reviewed			4	5

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☑No ☐N/A	74-day letter will include an IR for analytical methods and raw data
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
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)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
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?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code,	☑Yes ☐No ☐N/A	

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?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
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)?	☐Yes ☑No ☐N/A	74-day letter will include an IR for dose data for all studies
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General		
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9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

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/s/

CHRISTY S JOHN
11/17/2015

GENE M WILLIAMS
11/17/2015
I concur with the recommendations

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/s/

CHRISTY S JOHN
02/18/2016

GENE M WILLIAMS
02/18/2016
I concur with the recommendations

NAM ATIQUR RAHMAN
02/18/2016
I agree with the recommendation by the review team.

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