CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	(electronic stamp)
From	Lesley-Anne Furlong, MD, Deputy Director, Office of Drug Evaluation IV
Subject	Office Deputy Director Decisional Memo
NDA/BLA # **Supplement #**	208054
Applicant Name	Blue Earth Diagnostics LTD
Date of Submission	28-Sep-2016
PDUFA Goal Date	28-May-2016
Proprietary Name / Established (USAN) Name	Axumin/fluciclovine F18
Dosage Forms / Strength	Solution/370 MBq (10 mCi)
Applicant Proposed Indication(s)/Populations	For positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following prior treatment
Action:	Approval
Approved Indication(s)/Populations (if applicable)	N/A

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Phillip Davis, MD
Statistical Review	AG Mucci, PhD, Jyoti Zalkikar, PhD, Thomas Gwise, PhD
Pharmacology Toxicology Review	Yanli Ouyang, MD, PhD, Adebayo Laniyonu, PhD
OPQ Reviews Drug Substance	Benjamin Stevens PhD

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Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Drug Product Facility Environmental Assessment Microbiology Review	Ravidra Kasliwal, PhD Tony Wilson James Laurenson, PhD Eric Adeeku, PhD
Microbiology Review	Eric Adeeku
Clinical Pharmacology Review	CS John, PhD, GM Williams, PhD
OPDP	Amy Toscano, PharmD, and Adam George, PharmD (no comments)
CDTL Review	Nushin Todd, MD, PhD
DD Review/DMIP	Libero Marzella, MD, PhD
OSE/DMEPA	Michele Rutledge, PharmD and Yelena Maslov, Pharm D (strength statement on container labeling needs change); T Bridges RPh
OSE/DRISK	M Patel, Pharm.D; N Redd, PharmD, C LaCivita, PharmD
OPDP	Adam George, PharmD

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

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Statement of Concurrence with the Review Team

The review team unanimously recommended approval of this application. I have considered the reviews and concur with the conclusions of the review team.

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Axumin (fluciclovine F18) is a radioactive diagnostic agent indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment. Rising PSA levels can indicate recurrence well before clinical symptoms are evident. Optimizing therapy depends on accurate imaging to locate cancer recurrences.

Prostate cancer is a significant cause of morbidity and mortality in older men. According to the American Cancer Society, prostate cancer is the second leading cause of death from cancer in U.S. men, with approximately 26,000 U.S. deaths in 2016. The average age of diagnosis is 66 years. Up to one third of men treated with curative intent following a diagnosis of primary prostate cancer will experience recurrent disease within 10 to 15 years following therapy.

There have been two radioactive ligands approved by FDA for localizing recurrent prostate cancer. In111 capromab pendetide (ProstaScint), a single photon emission computerized tomography (SPECT) agent, was approved in 1999; however, its detection performance has limitations. In 2012, FDA approved choline C11 for PET imaging; however, choline C11's short half-life limits its use to medical centers with on-site production capability.

The evidence in this application supports efficacy of fluciclovine F18 for detection of prostate cancer recurrence in men with elevated PSA levels following prior treatment. Evidence of efficacy came from two published clinical trials: a pivotal trial from Emory University with a standard of truth (histologic verification) and a supportive trial from University of Bologna. For the NDA submission, fluciclovine F18 PET images were re-read by three blinded and independent readers and the data were re-analyzed by the applicant. The results of the independent reads were generally consistent with one another and confirmed the results of the on-site reads. From the Division Director memo: "The Emory Study evaluated 105 Axumin scans in comparison to histopathology obtained by biopsy of the prostate bed and biopsies of lesions suspicious by imaging. The study

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met its primary efficacy endpoint of positive predictive value and these results were consistent with multiple additional analyses of performance. At the subject level seven of ten patients with lesions detected by Fluciclovine F18 (71%) had prostatic cancer metastases and nearly all (97%) patients with metastases had Fluciclovine F18 detections verified as positive by histology." The point estimate of the detection rate (defined by the applicant as number of positive scans to total scans) in the pivotal study was higher at PSA levels greater than 1.78 ng/ml. While the authors of the published study from Emory University study concluded that Axumin had better diagnostic performance than ProstaScint, the reanalysis study was not designed to support comparative claims on labeling. The Bologna study was supportive of efficacy. Unlike choline C11, Axumin does not require on-site productions facilities.

The main safety issues are radiation exposure, hypersensitivity reactions, and image interpretation errors, which are class risks. Radiation exposure is comparable to that of other radiopharmaceuticals and between the radiation exposures from the two already approved products for the indication. Hypersensitivity reactions, while not observed in the safety database of 837 subjects, are reported for radiopharmaceuticals and may occur with Axumin; however, radiopharmaceutical drugs are administered in a setting where emergency medication, equipment, and personnel are readily available. Image interpretation errors occur with any imaging method; the proposed label describes the error rates observed in the clinical trials and recommends clinical correlation.

Considering the seriousness of the condition, the efficacy demonstrated in the clinical trials, and the risks, which are comparable to the risks of radiopharmaceuticals already approved for the indication, I concur with the team's unanimous recommendation for approval for use with final negotiated labeling. I agree with the team that a risk evaluation and mitigation strategy is not necessary.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	According to the American Cancer Society: • Prostate cancer is the second leading cause of death from cancer in U.S. men, with approximately 26,000 U.S. deaths in men in 2016. • The average age at the time of diagnosis is 66 years. • 1 in 7 men will be diagnosed with prostate cancer during his lifetime, and about 1 in 39 men will die of prostate cancer. • Men who have had prostate cancer are followed for recurrence using serum levels of prostate specific antigen (PSA) • Treatment options depend on the location of prostate cancer recurrence.	In the United States, prostate cancer is a significant cause of morbidity and mortality in older men. Recurrent prostate cancer can be detected, but not localized, by following blood levels of prostate-specific antigen (PSA). Optimal treatment is guided by location of prostate cancer recurrence.
Current Treatment Options	• Treatment of recurrent prostate cancer depends on location of recurrence and what treatment the patient has already undergone. • Imaging tests such as CT, MRI, PET scans, SPECT scans, and bone scans may be done to localize recurrence. • There are two FDA approved radioactive ligands for localizing recurrent prostate cancer. ProstaScint, a single photon emission computerized tomography (SPECT) agent, was approved in 1999, but its detection performance has limitations. In 2012, FDA approved Choline C11 for PET imaging, but Choline C11's short half-life limits its use to medical centers with on-site production capability.	Optimizing noninvasive ways to image recurrent prostate cancer is important because choice of treatment depends on location of recurrence. A radioactive ligand with good diagnostic performance for visualizing prostate cancer and an adequate half-life to allow for centralized production fills a gap in currently approved options for localizing recurrent prostate cancer.
Benefit	• Effective at identifying recurrent prostate cancer (both extra-prostatic recurrences and prostate bed recurrences) in a reanalysis of a published study from Emory University. Efficacy was shown by evaluating positive predictive value (PPV), and true and false positive and negative scans. It was not possible to measure the standard performance characteristics (sensitivity and specificity) because there was no 'standard of truth' that evaluated the subject's status	The evidence supports efficacy of fluciclovine F18 for detection of prostate cancer recurrence in men with elevated PSA levels following prior treatment.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	independently of histology evaluations of lesions that were detected by the imaging methods (including test and control images) that directed biopsies. Support of efficacy provided by a reanalysis of a published study from University of Bologna. • Less than one third of the radiation exposure of ProstaScint • 10-hour shelf life allows for centralized production and delivery of final drug product to the healthcare provider • As reported in the published study from Emory University with a truth standard (tissue biopsies), the lesion detection rates were numerically higher for Axumin compared with ProstaScint. FDA did not evaluate comparative claims because ProstaScint images were not re-read by blinded independent readers in the reanalysis.	
Risk	• Radiation exposure • False positives (FPs) and false negatives (FNs) occur • Detection rates for Axumin was better at PSA levels above 1.78 ng/ml, although data were limited at PSA levels lower than 1.78 ng/ml • Hypersensitivity reactions may occur with radiopharmaceuticals	• Radiation exposure is comparable to that of other radiopharmaceutical diagnostic agents (less than ProstaScint, more than choline C11). • FPs and FNs occur with other agents and the issue is addressed in labeling, which recommends clinical correlation. • Labeling adequately addresses the relationship between Axumin imaging and PSA levels • Drug is administered in centers where appropriate personnel and equipment is available and hypersensitivity reactions can be treated. This is a class

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The total safety database included 837 subjects with most subjects receiving a single dose. Adverse reactions were reported in less than 1% of subjects in clinical studies. The most common adverse reactions were injection site pain, injection site erythema, and dysgeusia (2 subjects). No deaths or serious adverse reactions were reported, although much of the safety data came from published studies. Duration of follow-up in the pivotal (Emory) study ranged from 7 to 35 days, which is acceptable for a microdose product intended for single dose administration.	effect. • The most common adverse reactions are not serious and reported in less than 1% of subjects.
Risk Management	• There were no risks identified for this product that would warrant a Risk Evaluation and Mitigation Strategy (REMS). According the DD summary review, 'diagnostic imaging agents as a class do not pose clinical risks that warrant the use of postmarketing risk management procedures.'	• Because the clinical studies did not identify an unexpected risk, routine postmarketing pharmacovigilance is recommended to assess postmarketing safety.

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2. Further discussion to support regulatory action

Background

Fluciclovine F18 is a new molecular entity developed as a diagnostic radiopharmaceutical. Fluciclovine is a synthetic L-leucine analog that enters preferentially into cancer cells where amino acid transporters are upregulated; it is not specific for prostate cancer cells.

The proposed drug product is an injectable solution administered as a microdose (no more than 10 micrograms of fluciclovine F18 in a single dose). It is indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment.

The application was granted a priority review designation because the drug product was judged to have the potential to improve the diagnostic accuracy for a serious condition for which an accurate diagnosis is important to optimize therapy.

Product Quality

Fluciclovine F18 for intravenous injection is supplied at the point of use as a sterile, clear, colorless solution in a 30 mL multiple dose vial containing 335-8200 MBq/mL at calibration time. Excipients include water, trisodium citrate, hydrochloric acid, and sodium hydroxide. The solution pH is between 4 and 6. The maximum mass dose of fluciclovine F18 is 10 micrograms (no more than 5 mL of a 2 microgram per ml solution.)

Drug substance, drug product, manufacturing process, microbiology, environmental assessments, sterility assessment, and manufacturing facilities were found acceptable by the OPQ review team. Axumin was granted a 10-hour shelf life under room temperature conditions. Labeling is consistent.

FDA inspected the manufacturing site for the nonradioactive precursor and the three drug product manufacturing sites. Inspection findings were acceptable. Three manufacturing sites have been designated. The NDA contains a protocol for adding new manufacturing sites for the drug product after approval.

The review team raised the concern that an impurity, (b) (4) could theoretically impact update of the active ingredient and asked the applicant to tighten the specification limits for the impurity. In an amendment submitted Jan 11, 2016[1] , the applicant agreed to reduce the specification limits for the impurity. The applicant agreed to investigate the feasibility of

[1]Page 29, responses to questions 34 and 35, eCTD Module 1.11.1.

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reducing the amount of the impurity (b) (4) in the drug product. The company agreed 'to report the results of the development work to the Agency, and discuss and agree future steps, within 12 months of NDA approval.' This was acceptable to the team. The CMC reviewer recommended that the agreement not be included in the approval letter as a postmarketing commitment because he did 'not view this as a PMC as defined under 506B.' After review of in vitro data, the clinical pharmacology team concluded that (b) (4) is unlikely to have any impact on the uptake of fluciclovine at the clinical dose. (See Clinical Pharmacology, below.) Based on the nonclinical pharmacology/toxicology and the clinical pharmacology reviews, there does not appear to be a safety or efficacy issue with (b) (4) within the specification limits proposed by the applicant, and I concur that the agreement does not need to be a PMC in the approval letter.

Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer found the nonclinical safety profile of fluciclovine and the major process impurity ((b) (4)) acceptable for approval. Safety pharmacology studies and general toxicology studies achieved high safety margins. Fluciclovine did not induce vascular irritancy in rabbits following intravenous injection. The active ingredient and (b) (4) were not mutagenic or clastogenic.

Clinical Pharmacology

The clinical pharmacology team recommended approval. No dose finding studies were submitted; however, a literature report from Oslo University concluded that doses of 200 MBq were ineffective. The reviewer also noted that the effective radiation dose resulting from administration of fluciclovine F18 is less than one third of that resulting from ProstaScint, a product currently marked for a similar indication. Pharmacokinetics were not assessed. Over 24 hours, 5.4% of administered radioactivity was excreted in the urine. The excretion profile could not be well characterized because excretion is measured by estimating radioactivity and the product was not detectable within 24 hours.

Although drug-drug interaction (DDI) studies were not performed, the reviewer deemed significant DDIs unlikely. The single microdose administered (no more than 10 micrograms/10 mCi) supports that fluciclovine F18 is unlikely to cause DDIs, and the trace amounts of metabolites detected in plasma and urine supports that fluciclovine F18 is unlikely to be affected by DDIs.

The impurity (b) (4) was unlikely to have any impact on the uptake of fluciclovine at the clinical dose. The maximum estimated concentrations of (b) (4) and fluciclovine in plasma are orders of magnitude lower than the concentrations at which the in vitro uptake of fluciclovine is saturated or inhibited by (b) (4). Review of ECGs from clinical studies did not show evidence of QT prolongation or other abnormalities.

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Clinical/Statistical – Efficacy

The clinical and statistical team have determined that the applicant provide substantial evidence of effectiveness.

The applicant evaluated the efficacy of fluciclovine F18 in reanalyses of data from two published studies: Study R01 performed at Emory University[2] and a supportive study performed at the University of Bologna.[3] Only the Emory study included histological confirmation of diagnosis ('standard of truth') and therefore it was considered pivotal by the review team.

Study R01 was an open label, prospective, single center study comparing fluciclovine F18 to the comparator, In 111 capromab pendetide (ProstaScint), in men with biochemical recurrence of prostate cancer following definitive treatment for local prostate cancer. Pathological evaluations of prostate bed and extraprostatic lesions were used as a standard of truth (SOT). The applicant obtained rights to the data and reanalyzed the study after a re-reading of images performed by three independent readers. A total of 105 Axumin scans were re-read and compared to histopathology obtained by biopsy of the prostate bed and biopsies of lesions suspicious by imaging. The following table summarized results by reader at both the patient level and the region level.

[2] Schuster et al. Anti-3-18F FACBC positron emission tomography-computerized tomography and 111In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: results of a prospective clinical trial. J Urol 191: 1446-1453, 2014
[3] Nanni, et al. 18F-fluciclovine PET/CT for the detection of prostate cancer relapse: a comparison to 11C-Choline PET/CT. Clin Nucl Med 40(8):386-391, 2015

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Table 1. Performance of Axumin in Patients with Biochemically Suspected Recurrent Prostate Cancer at the Patient Level and at the Region Level (Prostate Bed and Extraprostatic Regions)

	Reader 1	Reader 2	Reader 3
Patient	N = 104	N = 105	N = 99
True Positive	75	72	63
False Positive	24	23	13
True Negative	5	7	15
False Negative	0	3	8
Prostate Bed	N = 98	N = 97	N = 96
True Positive	58	56	47
False Positive	29	26	15
True Negative	10	12	24
False Negative	1	3	10
Extraprostatic	N = 28	N = 28	N = 25
True Positive	25	26	22
False Positive	2	2	2
True Negative	0	0	0
False Negative	1	0	1

N = number of patient scans evaluated

The CDTL notes that the original on-site-reads were very similar to the centralized re-reads. Although no comparisons were made to ProstaScint scans in the reanalysis, the CDTL also notes that, based on the original publication, there were 24 false negative fluciclovine scans and 56 false negative ProstaScint scans in subject with elevated PSA levels, supporting the utility of the new drug.

Axumin performance was better at PSA levels greater than 1 ng/ml, although data were limited because there were only 16 subjects who had PSA levels less than 1 ng/ml. The applicant assessed Axumin performance by PSA quartile. During my review, I noticed that the numbers in proposed labeling did not match the numbers in the MO reviews, which had come from Table 13 in the body of the applicant's clinical study report. The CDTL was able to resolve the discrepancy. The table in the body of the applicant's study report was incorrect because, when it was created from its source table (Table 14.2.3.9), two rows were mislabeled (reversed). The corrected table follows.

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Table 2. Performance of Axumin by PSA Quartile (Subject Level)

	PSA (ng/ml)			
	≤1.05	**>1.05 - ≤3.98**	**>3.98 - ≤8.90**	**>8.90**
N	16	31	25	27
True Positive	3	23	20	23
True Negative	8	3	1	0
False Positive	4	5	4	4
False Negative	1	0	0	0
PPV	42.9	82.1	83.3	85.2

Source: Table 14.2.3.9, eCTD Module 5.3.5.1, Study Report BED001-Emory

The performance of Axumin appears to drop off below a PSA of 1.05 ng/ml; however, the number of subjects is limited (N=16) in this range. On May 24, 2016, the applicant submitted the following two tables in response to an information request:

Table 3 Fluciclovine (^{18}F) PET-CT Scan Performance by PSA Quartile for the Histopath Population from the Emory Site Recurrent Prostate Cancer Population in BED-001 (Subject Level)

	PSA (ng/mL)			
	≤1.78	**>1.78 - ≤4.48**	**>4.48 - ≤9.25**	**>9.25**
No. subj in analysis	25	25	25	24
True Positive (%)	11	17	21	20
False Positive (%)	4	5	4	4
True Negative (%)	9	3	0	0
False Negative (%)	1	0	0	0
PPV [95%CI]	11/15 (73.3%) [44.9, 92.2]	17/22 (77.3%) [54.6, 92.2]	21/25 (84%) [63.9, 95.5]	20/24 (83.3%) [62.6, 95.3]
NPV [95% CI]	9/10 (90%) [55.5, 99.8]	3/3 (100%) [29.2, 100]	0/0	0/0
Sensitivity [95% CI]	11/12 (91.7%) [61.5, 99.8]	17/17 (100%) [80.5, 100]	21/21 (100%) [83.9, 100]	20/20 (100%) [83.2, 100]
Specificity [95% CI]	9/13 (69.2%) [38.6, 90.9]	3/8 (37.5%) [8.5, 75.5]	0/0	0/0
Detection Rate [95% CI]	15/25 (60%) [38.7, 78.9]	22/25 (88%) [68.8, 97.5]	21/25 (84%) [63.9, 95.5]	20/24 (83.3%) [62.6, 95.3]

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Table 4 Diagnostic Performance of Axumin at PSA Values above and below 2 ng/mL

	PSA≤2ng/mL	PSA > 2ng/mL
No. subj in analysis	28	71
True Positive (%)	13	56
False Positive (%)	5	12
True Negative (%)	9	3
False Negative (%)	1	0
PPV [95%CI]	13/18 (72.2%) [46.5, 90.3]	56/68 (82.4%) [71.2, 90.5]

Source of Table 3 and Table 4: eCTD Module 1.11.3, submitted 5/24/16

The point value of the PPV is lower at a PSA value less than 2 ng/ml (72.2%) compared with a PSA greater than 2 ng/ml (82.4%); however, the CI around the estimate is wide because the number of subjects is limited. A decline in performance is biologically plausible and expected based on experience with other imaging agents; however, the limited number of subjects providing data makes it difficult to define precisely where the drop-off in detection becomes problematic. For labeling, the applicant provided a brief summary of the data using detection rates defined as number with positive scans/total scans; the point estimate of detection rates was greater for the higher three PSA quartiles (71/74, or 96%) compared with the lowest PSA quartile (15/25, or 60%). False positive and false negative numbers for these groups were also provided in labeling. This was acceptable.

The Bologna study was generally supportive of the Emory study. The original published Bologna study evaluated the concordance between fluciclovine F18 and choline C11 scans (performed within one week) in patients with median PSA values of 1.44 ng/ml. The fluciclovine F18 scans were re-read by the same three blinded independent readers who re-read the scans for the Emory study, and the choline C11 scans were not re-read. The agreement between on-site reads and the 3 blinded reads was acceptable (78%, 61%, 67%, and 77% for the three readers) and the results were generally concordant with the results of the Emory study.

Safety

Safety was acceptable. A total of 837 subjects, including 12 healthy volunteers and 825 patients with cancer, were exposed to fluciclovine F18 in seven clinical studies. Doses ranged from 94 to 485 MBq, with most subjects receiving a single dose and approximately 370 MBq. Forty-four subjects received 2 doses, 3 subjects received 3 doses, 2 subjects received 4 doses, and 1 subject received 5 doses. Patients were followed for up to 35 days post injection. There were no deaths and no serious adverse reactions (SAEs) attributed to the drug. Laboratory data and ECGs did not detect a safety issue. The most frequently reported treatment emergent

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adverse events were injection site pain, erythema, and dysgeusia (2 subjects), each of which occurred in less than 1% of subjects.

Pediatrics

The applicant was granted a waiver from the requirement of the Pediatric Research Equity Act because prostate cancer does not occur in pediatric patients.

Labeling

Final negotiated labeling is acceptable.

Postmarketing Requirements and Commitments

The review team did not recommend postmarketing commitments, postmarketing requirements, or a risk evaluation and mitigation (REMS). I concur.

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/s/

LESLEYANNE FURLONG
05/26/2016