

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208054Orig1s000

SUMMARY REVIEW

Division Director Summary Review
 NDA 208054, Axumin (Fluciclovine F 18)
 Libero Marzella MD, PhD

Division Director Summary Review for Regulatory Action

Date	5/10/2016
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA/BLA #	208054
Supplement #	0
Applicant	Blue Earth Diagnostics Ltd
Date of Submission	9/28/2015
PDUFA Goal Date	5/27/2016
Proprietary Name / Non-Proprietary Name	Axumin Fluciclovine F18
Dosage Form(s) / Strength(s)	Injection 26 mL solution of 335-8200 MBq/mL (9-221 mCi/mL fluciclovine F 18
Applicant Proposed Indication(s)/Population(s)	PET imaging of men with suspected prostate cancer recurrence based on elevated PSA levels
Action/Recommended Action for NME:	Recommend approval
Approved/Recommended Indication/Population(s)	Axumin 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.

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Phillip Davis MD

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Statistical Review	Anthony Mucci PhD
Pharmacology Toxicology Review	Yanli Ouyang MD PhD
OPQ Reviews: Drug substance Drug Product (DP) Facility Environmental assessment	Benjamin D. Stevens PhD Ravindra K. Kasliwal PhD Tony Wilson James Laurenson PhD
Microbiology Review	Eric Adeeku PhD
Clinical Pharmacology Review	Christy John PhD
CDTL Review	Nushin Todd MD, PhD
Labeling Review	Michele Fedowitz MD
OPDP	Adam George PharmD
OSE/DMEPA	Michelle Rutledge PharmD
OSE/DRISK	Mona Patel PharmD

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 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

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Recurrence of prostate cancer after treatment with curative intent of the primary cancer is an important public health concern. Often the only evidence of recurrence is a rise in the levels of prostate specific antigen and standard imaging modalities fail to localize the site of recurrence. New imaging modalities are needed to improve the accuracy and early detection of cancer recurrence. Improvements in diagnostic performance are important to guide patient management and improve clinical outcomes.

Fluciclovine F -18 is a radiolabeled amino acid analogue designated as a new molecular entity in the diagnostic radiopharmaceutical product class for use with positron emission tomography imaging. Fluciclovine F 18 is transported across cell membranes by amino acid transporters that are upregulated in cancer cells. Fluciclovine F 18 is taken up to a greater extent in prostate cancer cells compared with surrounding normal tissues.

The efficacy of Axumin was evaluated in two studies in men with suspected recurrence of prostate cancer based on rising PSA levels following radical prostatectomy and/or radiotherapy. I relied on a study conducted at Emory University (published by Schuster et al, J Urol 191: 1446-1453, 2014) for the primary evidence of efficacy and on a second study conducted at the University of Bologna (published by Nanni et al, Clin Nucl Med, 40 (8): 386-391, 2015) for supportive efficacy. The Applicant re-analyzed the studies and conducted blinded, independent, re-reads of the images to verify the original clinical site interpretation of the images.

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 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%) patient with metastases had Fluciclovine F 18 detections verified as positive by histology. The performance of Axumin is affected by PSA levels. Among the 16 scans in patients with PSA levels less than or equal to 1 ng/mL, there were 4 false positive scans and 1 false negative scan. Among the 83 scans in patients with PSA levels greater than 1 ng/mL, there were 13 false positive scans and no false negative scans. The results of the independent reads were generally consistent with one another and confirmed the results of the on-site reads. The Bologna study evaluated the concordance between 96 Axumin and Choline C 11 scans. The agreement values between the Axumin and Choline C11 reads were 61%, 67% and 77% respectively. I conclude that the studies establish the utility of Fluciclovine F 18 for the detection of metastases of prostatic cancer in patients with recurrent disease.

The risks of Axumin are associated with radiation exposure and with image interpretation errors. Axumin use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Incorrect image interpretation is possible because. Fluciclovine F 18 uptake is not specific for prostate cancer and may occur with other types of cancer and benign prostatic hypertrophy in primary prostate cancer. Therefore a positive image does not confirm the presence of recurrent prostate cancer and a negative image does not rule out the presence of recurrent prostate cancer. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, is recommended.

Given the clinical importance of early and accurate detection of metastatic disease in patients suspected of having recurrent prostatic cancer, the

risks are acceptable. I conclude that the risk benefit of Fluciclovine F 18 is favorable and recommend approval of this new drug application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Patients who have undergone curative treatment of primary carcinoma of the prostate by radical prostatectomy or radiotherapy are followed clinically by testing that includes the measurement of prostate specific antigen (PSA). Patients who develop elevated PSA are suspected of having cancer recurrence. Localization of the recurrent cancer is critical for patient management and prognosis. • Prostatic cancer is the second most commonly diagnosed cancer in the US. It is estimated that ten percent of patients experience cancer recurrence after primary treatment. Accurate staging is an important objective in improving management and outcomes in primary and recurrent cancer. 	<p>Primary and recurrent prostatic carcinoma is a major public health issue in the US.</p>
Current Treatment Options	<ul style="list-style-type: none"> • Magnetic resonance imaging, computed tomography ultrasonography, single photon emission tomography and positron emission tomography are imaging procedure that might be done to localize recurrent prostatic cancer. • Blind biopsy of the prostatic bed region, lesion biopsy directed by findings on one or more imaging modality and clinical follow up are used to localize and verify the recurrence of the tumor and to develop a patient management plan. • The diagnostic accuracy of standard imaging for tumor detection is low. Enhanced performance characteristics and greater commercial distribution potential than provided by the currently marketed radiopharmaceuticals are needed. 	<p>The standard imaging modalities have limitations. New diagnostic options are needed for this serious condition.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> The data analyses from two prospective studies in the original publications and the re-analyses performed after blinded central interpretation of the Axumin images yielded favorable and consistent results. The Emory study provided acceptable estimates of positive predictive values (PPV) and lesion detection rates compared to a histology truth standard. However PPV is influenced by the prevalence of disease (70%). The truth standard is dependent on lesions detected by test, active control, or other imaging introducing verification bias and difficulty in verifying true negative status. The Bologna study provided supportive evidence of concordance of Axumin and Choline C11. Accurate staging of prostatic cancer in primary and recurrent prostatic cancer is an important medical need. Insufficient information was presented to establish that no important differences in tumor detection exist between patients with primary and patients with recurrent cancer. Both efficacy studies of Axumin included an active diagnostic comparator. (b) (4) In the study that included a truth standard, the lesion detection rates were numerically higher for Axumin compared to 111In-capromab pendetide. 	<p>Standard accuracy measures (sensitivity and specificity) cannot be used to evaluate cancer recurrence. PPV met its prespecified threshold but the estimate is influenced by disease prevalence. “Sensitivity” defined as proportion of patients with histology positive lesions who had these lesions detected by fluciclovine was very high. The most meaningful data are considered to be patient and region-level estimates of true positive and false negative rates as determined by central readers. (b) (4)</p> <p>(b) (4)</p>
Risk	<ul style="list-style-type: none"> Radiation exposure, misinterpretation of clinical images, hypersensitivity reactions are the most important safety concerns. Axumin contributes to a patient overall radiation exposure. Long term cumulative exposure increases the risk of cancer. The effective radiation absorbed dose is approximately 6 mSV. 	<p>The radiation exposure is consistent with that of other radiopharmaceutical diagnostic agents. Dosimetry tables will be provided in the labeling.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> Image interpretation errors can occur with Axumin PET imaging. A negative image does not rule out the presence of recurrent prostate cancer and a positive image does not confirm the presence of recurrent prostate cancer. Fluciclovine F 18 uptake is not specific for prostate cancer and may occur with other types of cancer and benign prostatic hypertrophy in primary prostate cancer. 	<p>Imaging results need to be verified by additional clinical testing including histology; the labeling will address this risk</p>
<p>Risk Management</p>	<ul style="list-style-type: none"> Diagnostic imaging agents as a class do not pose clinical risks that warrant the use of postmarketing risk management procedures. 	<p>No action is needed</p>

2. Background

On September 28, 2015 the Applicant (Blue Earth Diagnostics Ltd) submitted a 505(b)(1) new drug application (NDA) for the new molecular entity Fluciclovine F 18. This diagnostic radiopharmaceutical is proposed for use in PET imaging of men with suspected prostate cancer recurrence based on elevated PSA levels. This review summarizes my assessment of the approvability of the NDA.

Fluciclovine F 18 (b)(4) at Emory University and was subsequently developed as a PET radiopharmaceutical by (b)(4) and GE Healthcare. The Applicant acquired the rights to the data and did not conduct new preclinical studies or new clinical trials.

The clinical reviewer (Dr. Davis) and the cross discipline team leader (Dr. Todd) provide an overview of the public health importance of the clinical condition, namely prostatic cancer recurrence after curative therapy of a primary prostate cancer. The study patients are men who experience cancer recurrence based on rising prostate specific antigen (PSA) levels and who have negative standard diagnostic imaging studies.

The application was granted a priority review status because Fluciclovine F 18 was judged to have the potential to improve the diagnostic accuracy for a serious condition for which an accurate diagnosis is critical for patient management and improved outcome.

Standard imaging modalities for evaluation of recurrence have generally low accuracy. The clinical reviewers summarize the available diagnostic options including the two radiopharmaceuticals indicated for use in this patient population. Indium 111 capromab pendetide (Prostascint), a single photon emission computerized tomography (SPECT) agent, was approved in 1999 for the diagnostic imaging of patient with primary prostate cancer at high risk of metastasis and in patient with a rising PSA post-prostatectomy. PET imaging with Choline C 11 was approved in 2012, for use in patients with suspected prostatic cancer recurrence; however, the 20 minute half-life of ¹¹C limits the use of this agent to medical centers with on-site ¹¹C production capability.

There were no major scientific disagreements with the Applicant. The applicant reached agreement with the Division in pre-submission meetings on how to verify the results of the image interpretation performed on-site site for each of two prospective independent published studies for which they acquired the rights.

There was general agreement among all the primary and secondary reviewers regarding the overall adequacy of quality information and of data from preclinical and clinical studies.

The efficacy study design considerations and analyses for Axumin are typical for diagnostic medical imaging products. No major statistical analysis issues arose during the review and no important safety issue were identified. There are no class effects of particular concern for the product. No non-clinical safety signals, novel or incompletely resolved safety concerns were

identified. No postmarketing requirements and no risk evaluation and mitigation strategies are needed.

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

3. Product Quality

I concur with the CMC reviewer Dr. Kasliwal that all the quality aspects, i.e., the drug substance, the drug product, the manufacturing process, the microbiological aspects and the environmental assessment have been fully reviewed and are found to be adequate to support approval of the application.

The drug substance, fluciclovine F 18, is produced as an aqueous solution (b) (4)

(b) (4) The CMC reviewer considers the products of the (b) (4) modules to be equivalent.

The manufacturing site for (b) (4) the three drug product manufacturing site were inspected for conformity with cGMP. The review of the manufacturing facilities has been completed and no significant risks were identified. The final recommendation that the facilities are adequate for the operations proposed in the submission was issued. The NDA contains (b) (4) for the manufacture of fluciclovine F18 injection drug product subsequent to the approval of the NDA.

The proposed proprietary name for the product is Axumin. Fluciclovine (18F) is the International Non-proprietary Name for the active substance *anti*-1-amino-3-[18F] fluorocyclobutane-1-carboxylic acid. Fluciclovine F 18 is the proposed United States Approved Name (USAN).

I concur with the recommendation by Dr. Adeeku that sufficient sterility assurance has been provided. The PET drug product is a sterile unpreserved solution for intravenous administration. Three manufacturing sites have been designated. No microbiology deficiencies were identified.

4. Nonclinical Pharmacology/Toxicology

I concur with the recommendation by the pharmacology/toxicology reviewer Dr. Ouyang that the application be approved based on adequate nonclinical safety evaluations and the safety profile for the intended use.

Fluciclovine F 19, a non-radioactive formulation of the fluciclovine F 18 injection drug product with an equivalent impurity profile, was used in nonclinical studies. Dr. Ouyang summarizes the pharmacology toxicology findings as follows.

Process impurity

The major issue was the presence of an impurity ((b) (4)) in the drug product. Nonclinical safety of the impurity was evaluated in the nonclinical studies conducted for anti-FACBC formulation (containing (b) (4)) or for (b) (4) alone. The lot used in the 14 day repeat dose toxicity studies contained 1.8 mcg/mL anti-FACBC and (b) (4) . The calculated ratio of anti-FACBC/ (b) (4) was (b) (4) . The NOAELs for (b) (4) are calculated using this ratio based on NOAELs for anti-FACBC. Adequate safety margins for (b) (4) were established (HMD (b) (4)).

Irritancy

Paravenous injection of fluciclovine induces pain and mild inflammation in the subcutaneous tissues. In a study in rabbits 3 of 6 animals struggled vigorously during and immediately after subcutaneous injection of cold fluciclovine. This reaction was attributed to pain caused by low pH (3.1) and high osmotic pressure (515 mOsm/kg). In addition, slight cellular infiltration in the subcutis was noted and resolved by Day 14. On the other hand, fluciclovine did not induce vascular irritancy in rabbits following intravenous injection. No hemolytic activity was identified. The Applicant agreed to change pH to 4 upon the FDA's recommendation.

Pharmacology

[14C]-FACBC uptake peaked at 5 to 30 minutes in five human prostate adenocarcinoma cell lines. The uptake by the cancer cell lines was higher than that by normal human prostate epithelial cell line at early time points (2 to 9 times higher at 5 and 15 minutes). 18F-anti-FACBC in tumor bearing mice achieved the highest tumor/tissue ratios at 5 minutes post-dosing.

Safety pharmacology

In hERG assays, 1×10^{-6} mol/L (the highest concentration tested) of anti-FACBC had minimal effect on the hERG current amplitude compared with the controls (91% of the control value). Intravenous administration of 43 mcg/kg FACBC in rats produced no remarkable effect on behavior, body temperature, and respiratory function. Intravenous infusion of 5.4 mcg/kg FACBC to conscious dogs did not elicit biologically significant changes in blood pressure, heart rate, ECG, and QTc interval.

Following a single intravenous injection of anti-[18F]FACBC in rats, the highest concentration of radioactivity was found in the pancreas, thymus gland, kidneys, muscle, stomach, and bone marrow. Anti-[18F] FACBC was mainly excreted through urine. Anti-[14C] FACBC or anti-[18F] FACBC was not metabolized in vivo (less than 5%) and in vitro in rat, dog, monkey, or human liver microsomes.

General toxicology

Fourteen day intravenous toxicity studies of anti-FACBC in rats and dogs established NOAELs at 22 and 10.8 mcg/kg/day respectively (dose multiples of 21X or 35X based on body surface area).

Genetic toxicology

Both anti-FACBC (the active ingredient) and (b) (4) (the major impurity) were negative in the in vitro reverse mutation assay in bacteria (Ames), in the in vitro chromosomal aberration assay, and in vivo micronucleus assay.

5. Clinical Pharmacology

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

Mechanism of action

Fluciclovine F 18 is a synthetic amino acid transported across mammalian cell membranes by amino acid transporters, such as LAT-1 and ASCT2, which are upregulated in prostate cancer cells. Fluciclovine F 18 is taken up to a greater extent in prostate cancer cells compared with surrounding normal tissues.

Pharmacodynamics

Following intravenous administration, the tumor-to-normal tissue contrast is highest between 4 and 10 minutes after injection, with a 61 % reduction in mean tumor uptake at 90 minutes after injection

Pharmacokinetics and metabolism

Fluciclovine F 18 does not undergo significant metabolism. There was no measurement of active moieties in any of the studies on imaging performance.

Assessment of Fluciclovine F 18 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 four organs with the highest initial uptake of ¹⁸F were the liver (14%), red bone marrow (11 %), lung (7%), and pancreas (4%). 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.

Recommended dose

Clinical trials from various institutions (Oslo University, Bologna University, and Emory University) studied doses of ¹⁸F-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

Fluciclovine F 18 is 2 mcg/mL (max of 10 mcg). While there is no assurance that an optimal dose has been identified, the proposed dose is effective.

Process impurity

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 amino acid transporter is much lower than that of fluciclovine. The impurity is similarly not incorporated into 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 2mcg/mL (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 15nM (b) (4) respectively, which are orders of magnitude lower than the concentrations at which the in vitro uptake of fluciclovine is saturated (Km of 64mcM) or inhibited by (b) (4) (IC50 of (b) (4)).

The effective radiation dose resulting from the administration of 370 MBq Fluciclovine F 18 for an adult weighing 75 kg is approximately 6 mSv. A comparable effective dose for Choline C 11 is 2.6 mSv and the effective dose for Indium 111 capromab pentetide is 27 mSv.

QT effects

The mass of Fluciclovine F 18 injected is about 10 mcg. The drug is injected only once, thus the likelihood of QT or QTc prolongation is remote. There were no significant effects of 18Ffluciclovine injection on ECG interval changes in mean values or shifts from baseline in ECG parameter.

Food effects

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. 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. In the clinical studies patients fasted (4 hrs) before the administration of Fluciclovine F 18.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

I concur with the clinical and statistical reviewers' assessment that in men with recurrent prostate cancer Fluciclovine F 18 is useful for the detection of metastases as verified by histopathology and patient follow up.

The primary and secondary clinical reviewers (Dr. Davis and Dr. Todd) and the primary and secondary statistical reviewers (Dr. Mucci and Dr Zalkikar) focused their reviews on a study conducted at Emory University (published by Schuster et al, J Urol 191: 1446-1453, 2014) for the primary evidence of efficacy and on a second study conducted at the University of Bologna (published by Nanni et al, Clin Nucl Med, 40 (8): 386-391, 2015) for supportive efficacy. The Applicant conducted re-analyses of the studies and conducted blinded, independent, centralized re-reads of the images to verify the original clinical site interpretation of the images.

The reviewers agreed in their assessment of the Emory study and in the importance of various primary and secondary efficacy analyses for demonstrating utility. The reviewers evaluated several performance characteristics and found them generally consistent with each other. The reviewers highlighted the following aspects.

- Value of histology as truth standard to validate lesion detection
- Lack of independent ascertainment of truth standard precludes the use of standard accuracy measures (sensitivity and specificity) to evaluate cancer recurrence
- Re-read of images in a blinded fashion useful to validate the image interpretation at the clinical site
- Most clinically useful definition of efficacy is with respect to subject and anatomic region classifications for recurrence of disease
- Weakness of positive predictive value as a primary endpoint due to influence of this estimate on the prevalence of disease.
- Need to couple positive predictive value with a measure that lesion detections are generally positive by histology
- Consistency of favorable results among the initial study publication, the re-analysis study and the re-read study
- The labeling will provide subject and region levels summary statistics showing true/false positive and negative lesion detections

The Emory study met its primary efficacy endpoint of PPV. Dr Mucci determined that at the subject level seven of ten patients (71%) with lesions detected by Fluciclovine F 18 had prostatic cancer metastases and nearly all (97%) patient with metastases had Fluciclovine F 18 detections verified as positive by histology. I agree with the reviewer that these results are persuasive. Dr. Davis points out that the original publication showed Fluciclovine F 18 detected more lesions than the active comparator. Table 1 summarizes the principal efficacy outcomes of the Emory study.

Table 1: Performance of Axumin in Patients with Biochemically Suspected Recurrent Prostate Cancer, at the Patient Level and in the Prostate Bed and Extraprostatic Regions Levels

	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 performance of Axumin is affected by PSA levels. Among the 16 scans in patients with PSA levels less than or equal to 1 ng/mL, there were 4 false positive scans and 1 false negative scan. Among the 83 scans in patients with PSA levels greater than 1 ng/mL, there were 13 false positive scans and no false negative scans.

I agree with the FDA reviewers that the study conducted at the University of Bologna is generally supportive. The study evaluated the concordance between 96 Axumin and Choline C 11 scans in patients with median PSA value of 1.44 ng/mL (interquartile range = 0.78 to 2.8 ng/mL). The Choline C 11 scans were read by on-site readers. The Axumin scans were read by the same three blinded independent readers used for the reread of the Emory study. The agreement values between the Axumin and Choline C11 reads were 61%, 67% and 77% respectively.

8. Safety

I concur with Dr. Davis' assessment that in the intended population and clinical use, the safety database of 877 subjects, including 797 men diagnosed with prostate cancer is adequate to assess the safety of Fluciclovine F18 injection. Most patients received a single administration of Axumin, a small number of subjects (N = 50) received up to five administrations of the drug. The mean administered activity was 370 MBq. Safety evaluations included treatment emergent adverse events, pre and post treatment changes in laboratory hematology,

biochemistry and urinalysis, safety evaluations, pre and post treatment 12 lead ECGs, as well as vital signs pre and post dose during imaging sessions. No deaths or serious adverse reactions were reported. Adverse reactions occurred in < 1% study subjects. The most common were injection site pain and dysgeusia.

The risks of Axumin are associated with radiation exposure and with image interpretation errors. Axumin use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. A negative image does not rule out the presence of recurrent prostate cancer and a positive image does not confirm the presence of recurrent prostate cancer. The performance of Axumin is affected by PSA levels. Fluciclovine F 18 uptake is not specific for prostate cancer and may occur with other types of cancer and benign prostatic hypertrophy in primary prostate cancer. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, is recommended. Hypersensitivity reactions including anaphylaxis are a potential risk in patients who receive Axumin. Emergency resuscitation equipment and personnel should be immediately available.

9. Advisory Committee Meeting

The application did not raise regulatory or scientific issues. The approval of another radiopharmaceutical (Choline C 11) was based on similar study design and endpoint (lesion localization rates verified by histopathology) in the same patient population (patients with elevated PSA levels suspected of cancer recurrence). For these reasons no advisory committee meeting was necessary.

10. Pediatrics

The Applicant requested a waiver. Prostate cancer is most frequently diagnosed among older men with median age at diagnosis as 66 years. Therefore, pediatric studies were waived based on the indicated population.

11. Other Relevant Regulatory Issues

I concur with the assessment by Dr. Rutledge that the proposed proprietary name does not misbrand the product or raise concerns about the potential for medication errors.

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

12. Labeling

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

- **INDICATIONS AND USAGE section:**
I agree with the Applicant on the indicated population namely patients with recurrent prostate cancer based on elevated levels of PSA after primary treatment. Broadening the indicated population to include patients with [REDACTED] (b) (4) [REDACTED] was considered. However insufficient supportive information on diagnostic performance of Axumin in patients [REDACTED] (b) (4) prostate cancer was available. An adequate study of Axumin in patients [REDACTED] (b) (4) [REDACTED] could provide the necessary performance data. No limitations for use statements were considered necessary.
- **DOSAGE AND ADMINISTRATION section:**
The recommended dose is effective. However no dose ranging studies were performed to optimize the Axumin dose.
- **WARNINGS AND PRECAUTIONS sections:**
The risks associated with Axumin are due to radiation absorbed dose from the F 18 radioisotope and errors in image interpretation. These risks are described in the warnings section. It is also mentioned that interpretation of the scans is dependent on PSA levels.
- **CLINICAL STUDIES section:**
The Emory study was the principal efficacy study establishing the diagnostic performance of Axumin. The most important diagnostic information was considered to be the Axumin cancer detection rate at the patient level defined as the proportion of true positive patients among the true positive and false negatives. Performance at the region level (prostate bed and extraprostatic bed) was also presented. Performance at the lesion level was not included as it did not add more useful clinical information. Only the results of the blinded reads were presented because the results were similar to those of the site readers and provided information on the level of agreement of the readers. [REDACTED] (b) (4) [REDACTED]

13. Postmarketing

A review by The Division of Risk Management (DRISK) determined whether a risk evaluation and mitigation strategy (REMS) for this new molecular entity (Axumin, fluciclovine) is necessary to ensure the benefits of this product outweigh its risks. As a class, diagnostic radiopharmaceuticals have not required a REMS for approval. The applicant did not submit a proposed REMS or risk management plan with this application. I concur with Dr.

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Patel's assessment that none are needed.

I concur with the recommendation by the CMC and Pharmacology/Toxicology reviewers that the applicant investigate the feasibility of reducing the amount of the process impurity (b) (4) in the drug product. The Applicant has agreed (Jan 11 2016 amendment) to perform preliminary development work and to report the results to the Agency. The objective is to achieve a reduction within 12 months of NDA approval. Based on the data from 21 batches made by the final manufacturing process, the (b) (4) concentrations were much lower (range: (b) (4)). Therefore the CMC team proposed specification of (b) (4) as (b) (4) is reasonable.

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/s/

LIBERO L MARZELLA
05/10/2016