

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208054Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208054
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Reviewer Name(s)	Mona Patel, Pharm.D.
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Division Director	Cynthia LaCivita, Pharm.D., Division Director
Review Completion Date	February 21, 2016
(Date DARRTED)	
Subject	Evaluation to determine if a REMS is necessary
Established Name	fluciclovine
(Proposed) Trade Name	Axumin
Applicant	Blue Earth Diagnostics Ltd
Formulation	injection
Dosing Regimen	370 MBq (10 mCi) administered as (b) (4) intravenous injection
Proposed Indication(s)	diagnostic agent for positron emission tomography imaging of men with suspected prostate cancer recurrence.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Axumin (fluciclovine) is necessary to ensure the benefits of this product outweigh its risks. Blue Earth Diagnostics submitted a New Drug Application (NDA 208054) for fluciclovine with the proposed indication as a radioactive diagnostic agent for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence. The risks associated with the use of fluciclovine are radiation exposure. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Medical Imaging Products agree that a REMS is not needed to ensure the benefits of fluciclovine outweigh its risks.

1 Introduction

Blue Earth Diagnostics submitted a New Drug Application (NDA) for fluciclovine with the proposed indication as a radioactive diagnostic agent for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION¹

Axumin (fluciclovine) is a diagnostic radiopharmaceutical, and is not used to treat any disease or medical condition. This product is a synthetic amino acid transported across mammalian cell membranes by amino acid transporters such as LAT-1 and ASCT2. These have been shown to be up-regulated in many cancer cells. The applicant's proposed indication is for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence.

The recommended radioactivity to be administered is a (b)(4) intravenous injection of 370 MBq (10 mCi). Fluciclovine is supplied in 30 mL multidose vials containing approximately 26 mL of a clear, colorless solution at a strength of 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine 18 F at calibration time and date. The drug product will be administered for in-patient use only. This is a NME 505 (b)(1) application under Priority review with a PDUFA date of May 27, 2016. The efficacy of this product is based on two prospective open label studies of fluciclovine. Fluciclovine is not currently licensed in any jurisdiction. Fluciclovine is not part of a class of drugs that has a REMS or a Boxed Warning.

¹ Blue Earth Diagnostics Proposed Labeling for Axumin (fluciclovine) December 4, 2015

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208054 relevant to this review:

- 4/30/2010: IND 107707 active
- 6/26/14: Type C meeting to discuss clinical program
- 2/2/15: Type C Meeting to discuss statistical plan for BED-001
- 2/26/15: Type C Meeting to discuss statistical plan for BED-002
- 09/28/2015: NDA 208054 submission received for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence
- 10/9/2015: Agreed Initial Pediatric Study Plan
- 1/6/2016: Midcycle Meeting

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION²

Prostate cancer is the most commonly diagnosed non-cutaneous neoplasm in men in the United States. In 2015, it was estimated that 1 in 7 men will be diagnosed with prostate cancer and there is expected to be approximately 220,800 new cases and 27, 540 deaths from the disease. It is the second leading cause of cancer death in American men, behind lung cancer. This cancer is very rare in men younger than 40, but the chance of having prostate cancer rises rapidly after age 50. The average age at diagnosis is 66 years old and about 6 in 10 cases of prostate cancer are found in men over the age of 65. According to the National Cancer Institute's SEER database, between 2005-2011, the 5-year survival rate for patients diagnosed with prostate cancer was 98.9%. The diagnostic accuracy of standard imaging tests for the identification of sites of recurrence is low. Almost 90% of the standard battery of imaging tests, including CT/MRI and bone scintigraphy, may be negative; for this reason more accurate, non-invasive imaging techniques for the detection of recurrent tumor is needed.³

3.2 DESCRIPTION OF CURRENT DIAGNOSTIC OPTIONS

¹¹¹Indium capromab pentetide (*Prostascint*), a single photon emission computerized tomography (SPECT) agent, was approved in 1999 for the diagnostic imaging of post-prostatectomy patients with a rising PSA, but this procedure has been largely superseded by PET imaging agents. The glucose analogue *Fludeoxyglucose F 18 (FDG)* was originally approved in 1994 and is the most widely used PET radiotracer, with established utility in a wide variety of tumour settings. FDG is not generally used as an imaging agent in prostate cancer, due to indolent growth of many

² <http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics>

³ Choueiri TK, Dreicer R, Paciorek A, Carroll PR, Konety B. A model that predicts the probability of positive imaging in prostate cancer cases with biochemical failure after initial definitive local therapy. *J Urol.* 2008 Mar;179(3):906-10

prostate cancers and the high urinary excretion of FDG making reliable, good quality imaging difficult in this patient population. Alternative radiotracers with different mechanisms of action that could overcome these limitations have therefore been sought. PET imaging with Choline C-11, approved in 2012, has been shown to improve detection of cancer recurrence in men with BCR prostate cancer and is approved for clinical use. As a class, diagnostic radiopharmaceuticals do not have a Boxed Warning in their respective labels and have not required a REMS for approval.

The table below summarizes these diagnostic modalities.

Table 1: Summary of Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic)	Year of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Bo xed Warning, Medication Guide
<i>¹¹¹Indium capromab pentetide (Prostascint®)</i> ⁴	1996	for newly-diagnosed patients with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation who are at high-risk for pelvic lymph node metastases; also indicated as a diagnostic imaging agent in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease.	0.5 mg radiolabeled with 5mCi of Indium In 111 chloride by intravenous injection	Allergic hypersensitivity reactions	None
<i>Fludeoxyglucose F 18 (FDG)</i> ⁵	1994	Indicated in PET imaging for assessment of	185-370 MBq (5-10 mCi)	None	None

⁴ Prostascint (¹¹¹Indium capromab pentetide) US Package Insert (6/2012)

		abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnoses of cancer			
<i>Choline C 11</i> ⁶	2012	for PET imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging.	370 to 740 MBq (10 to 20 mCi) as a bolus IV injection	Mild injection site reactions (no numbers).	None

Of these agents listed in Table 1, Choline C 11 is the most similar to fluciclovine, since its indication is for those with suspected prostate cancer recurrence. Limiting factors with the use of Choline C 11 include greater patient preparation to take the drug by having to fast 6 hours prior to administration with Choline C 11 versus 4 hours with fluciclovine, higher radiation dose to patients, and possibly poorer image quality. When fluciclovine is added to PET scanning, lesion detectability is enhanced due to improved resolution of the images.

4 Benefit Assessment¹

⁵ Fludeoxyglucose F18 US Package Insert (1/2012)

⁶ Choline C 11 US Package Insert (9/2012)

The evidence of clinical benefit is based upon two prospective open label studies of fluciclovine. The clinical benefit of the product appears to be found in terms of increased sensitivity of the product over the currently approved products.

R01 Emory study was a prospective open label study of fluciclovine vs. indium capromab with histology reference standard (RT) in patients with suspected prostate cancer recurrence. The primary endpoint in this study was accuracy, as measured by positive predictive value (PPV) and negative predictive value (NPV) compared to indium capromab. The Bologna study was a prospective open label study comparing lesion detection rates of 18F-fluciclovine to Choline C 11 in patients with suspected prostate cancer recurrence. The primary endpoint in this study was detection rate (patient and lesion level). According to the sponsor's submission, six patients were positive with fluciclovine (18F) but negative with Choline C 11. No patients had a positive Choline C 11 scan with a negative fluciclovine (18F) scan. There was a statistically significant difference, in favor of fluciclovine, between the two tracers with respect to the number of positive scans. Schiavina et al reported that, in patient-based analyses, Choline C 11 PET-CT was positive in 23 patients and negative in 56 (DR 29.1%) while fluciclovine (18F) PET-CT was positive in 30 patients and negative in 49 (DR 37.9%) (Fisher's exact test $p < 0.001$). All lesions identified using Choline C 11 were also positive following fluciclovine (18F) PET-CT but an additional 18 lesions were identified on the fluciclovine (18F) images. On a lesion basis, Choline C 11 detected 38 lesions (15 bone, 12 lymph node, 11 local relapse), while fluciclovine (18F) detected 56 lesions (15 bone, 29 lymph node, 12 local relapse).⁷

In the Emory study of 93 subjects, overall, there was a 96.1% histological proof of positivity for anti-3-[18F] FACBC with a median patient follow up of 41 months. There were fewer false negatives with fluciclovine and more lesions found. Suspected recurrence was based on rising PSA. The median PSA value was 2.9 ng/mL (interquartile range 1.1; 8.9). The rate of detection of prostate cancer by fluciclovine was 80.3% compared to 53.5% with indium capromab. The subject level detection rate for the prostatic bed [34/71 (47.9%) vs 56/71 (78.9%)] and extraprostatic area [10/71 (14.1%) vs 22/71 (30.9%)] was significantly lower following use of indium capromab than following use of fluciclovine.

In the BED002 (Bologna) study of 88 subjects, overall, there were improved "detection rates" compared to Choline C 11. Patients in this study had previously undergone radical prostatectomy as their primary treatment and had suspected prostate cancer recurrence based on rising PSA. The median PSA value was 1.44 ng/mL (interquartile range 0.78-2.8 ng/mL). In the read of the images from this study at the clinical site, there was general concordance between fluciclovine and Choline C 11 PET (Kappa = 0.62; $p = 0.05$).

5 Risk Assessment & Safe Use Conditions^{1,4,6}

⁷ Schiavina, R Nanni, C, Brunocilla E, Pultrone CV, Zanonil, Borghesi M, Passaretti G, Vagnoni V, Martorana G, Fanti S. 18F-FACBC compared with 11C-choline PET/CT in patients with biochemical relapse after radical prostatectomy: A prospective study in 79 patients. P092 European Urology Supplements (13). 2014; p144.

There are very limited adverse events reported with use of fluciclovine. Injection site pain and erythema, headache and dysgeusia have been reported following administration of fluciclovine F 18. The Warnings and Precautions section of the label contain similar language that are found in all radiopharmaceuticals with limiting the exposure of radiation to the patient as much as possible, minimizing image interpretation errors, and monitoring for hypersensitivity reactions. Indium capromab has a similar safety profile, with the frequency of adverse events being found in 4% of 529 patients observed in clinical trials. These adverse events were mild and readily reversible and included: increases in bilirubin, hypotension, and hypertension. Elevated liver enzymes and injection site reactions occurred in slightly less than 1% of patients. For Choline C 11, exclusive of an uncommon, mild injection site reaction, no adverse reactions to Choline C 11 have been reported. None of the adverse events reported with fluciclovine or in the indium capromab or Choline C 11 labels rose to the level of a Boxed Warning. The risks under Warnings & Precautions for fluciclovine were class effects of the drug. Prostatecint along with fluciclovine included a contraindication for this drug product that it should not be used in patients who may be hypersensitive to the drug product or its excipients. The Warnings and Precautions section was under review at the time of this writing. This product is available in a 30 mL multidose vial, has a 109^(b)₍₄₎ minute half-life, and imaging is to be conducted 3-5 minutes after completion of the injection. Typical total scan time is between 20-30 minutes. These factors limit patient exposure to any potential risks.

6 Analysis of Expected Postmarket Use

Diagnostic radiopharmaceuticals are limited to inpatient settings and are prepared and administered by nuclear medicine physicians and staff with appropriate radiation training. Like other imaging drugs, fluciclovine will not be marketed to the general population which presents limited potential for off label use.

7 Discussion of Need for a REMS

Up to one third of patients treated with curative intent following a diagnosis of primary prostate cancer will experience recurrent disease within 10-15 years following primary treatment.⁸

Fluciclovine is a synthetic amino acid that is transported into mammalian cells by amino acid transporters (AATs), most notably LAT1 and ASC2 transporters. The indication for fluciclovine is as a radioactive diagnostic agent for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence. ¹¹¹Indium capromab pendetide and Choline C 11 are similar FDA approved products for the detection of primary or recurring prostate cancer. All of these products are given as a single IV dose for diagnostic use and have low incidences of adverse effects. The adverse effects that have been reported for both products were mild in intensity and Grade 1 and neither of the product labels have Boxed Warnings. However, the 20 minute half-life of Choline C 11 limits the use of this

⁸ Clinical Overview (section 2.5), Axumin (fluciclovine)

agent to medical centers with on-site ^{11}C production capability, which prevents this agent from being supplied via the established PET supply chain. The longer half-life (110 minutes) makes fluciclovine more practical for clinical use. Furthermore, fluciclovine appeared to have better sensitivity and specificity for lesion detection and better imaging results compared to indium capromab pendetide or Choline C 11.

As with other diagnostic radiopharmaceuticals, fluciclovine will be restricted to inpatient settings. This product will be prepared and given by nuclear medicine physicians and staff who are required to have specialized training for the handling and management of radionuclides as part of their daily clinical practice. Past regulatory actions have not required a REMS for approval of these types of products.

8 Conclusion & Recommendations

In conclusion, DMIP and DRISK agree that risk mitigation measures beyond professional labeling are not warranted for fluciclovine to ensure the benefits outweigh the risks. Healthcare providers who use radiopharmaceuticals for the detection of tumors are familiar with the risks associated with these products and understand the importance of patient monitoring. Should DMIP have any concerns or questions, or if new safety information becomes available that changes the risk: benefit profile of this product, please send contact DRISK.

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/s/

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