

New FDA-approved Diagnostic Imaging Agent for Identification of Recurrent Prostate Cancer “Fills the Gap”

Blue Earth Diagnostics developed a newly FDA-approved PET radiopharmaceutical to detect biochemically recurrent prostate cancer. Siemens' PETNET Solutions is the exclusive commercial supplier in the United States. Together, the two aim to improve patient management.

By Rhett Morici, Molecular Imaging Business Line, Siemens Healthcare

For prostate cancer, Blue Earth Diagnostics Ltd.'s purpose is precise: To find the site of biochemically recurrent disease.

“That’s what we do,” said Jonathan Allis, Chief Executive Officer at Blue Earth Diagnostics, a private diagnostics company focused on the development and commercialization of innovative positron emission tomography (PET) imaging agents to address unmet needs in cancer.

Prostate cancer is the second leading cause of cancer death in men in the United States (U.S.), and about 1 in 7

men will be diagnosed with the disease during their lifetime.¹ Routine blood screenings for prostate-specific antigen (PSA) can detect disease while still local to the prostate gland and can be treated in time. However, despite an oft-curative initial therapy, 20-30 percent of treated men will experience disease recurrence.²

It is not that simple, though. While recurrence of prostate cancer can be determined through PSA biochemical tests, knowing its location to inform patient management is less clear.

“The ways of locating the recurrence of prostate cancer are limited,” said Allis, who has a doctorate in biochemistry from Oxford University. “And finding the site or sites of recurrence can facilitate the most appropriate approach to patient management.”

Particularly in the U.S., imaging modalities like CT, MRI and ultrasound are used to find the site of recurrent disease. But detection rates have proven to be low.³ This lack of sensitivity may often lead to “algorithmic” treatment strategies.



“Patient management of biochemically recurrent prostate cancer is not typically personalized specific to the disease location, and is often based on an expectation of where it might be,” said Allis. “The ability to detect and determine the location of biochemically recurrent disease is the real opportunity to improve patient care.”

Enter Axumin™ (fluciclovine F 18)

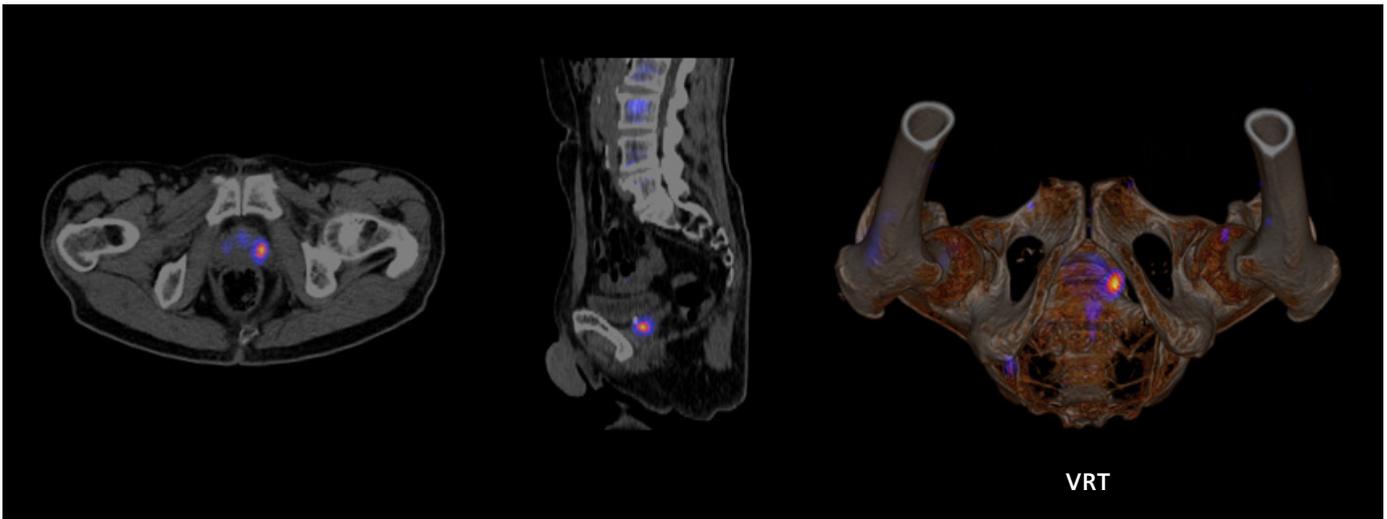
Molecular imaging is not commonly used to locate biochemically recurrent prostate cancer in the U.S. today, where use is limited due to a small number of effective and approved radiotracers. However, molecular imaging’s potential to detect biochemically recurrent prostate cancer is not to be written off. Rather, it is in this

void that Blue Earth Diagnostics plans to make its impact with Axumin (fluciclovine F 18).

Approved by the U.S. FDA on May 27, 2016, Axumin (fluciclovine F 18) injection is a fluorine-18-labeled synthetic amino acid indicated for PET imaging in men with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment. Since cancer cells, including prostate cancer, have increased uptake of amino acids relative to normal cells, Axumin can help identify the location of the recurrence. And the ¹⁸F-labeled radiopharmaceutical has a half-life which facilitates broader geographical distribution.

“The ability to detect and determine the location of biochemically recurrent disease is the real opportunity to improve patient care.”

Jonathan Allis, CEO, Blue Earth Diagnostics



Positive left prostate lobe.

Biograph mCT 40

Parameters: 67 y/o male, 70 kg (154 lb)

Data courtesy of Blue Earth Diagnostics Ltd.

“This is a big milestone. The PET industry has been waiting for new oncology biomarkers for years.”

Barry Scott, Head of Siemens' PETNET Solutions

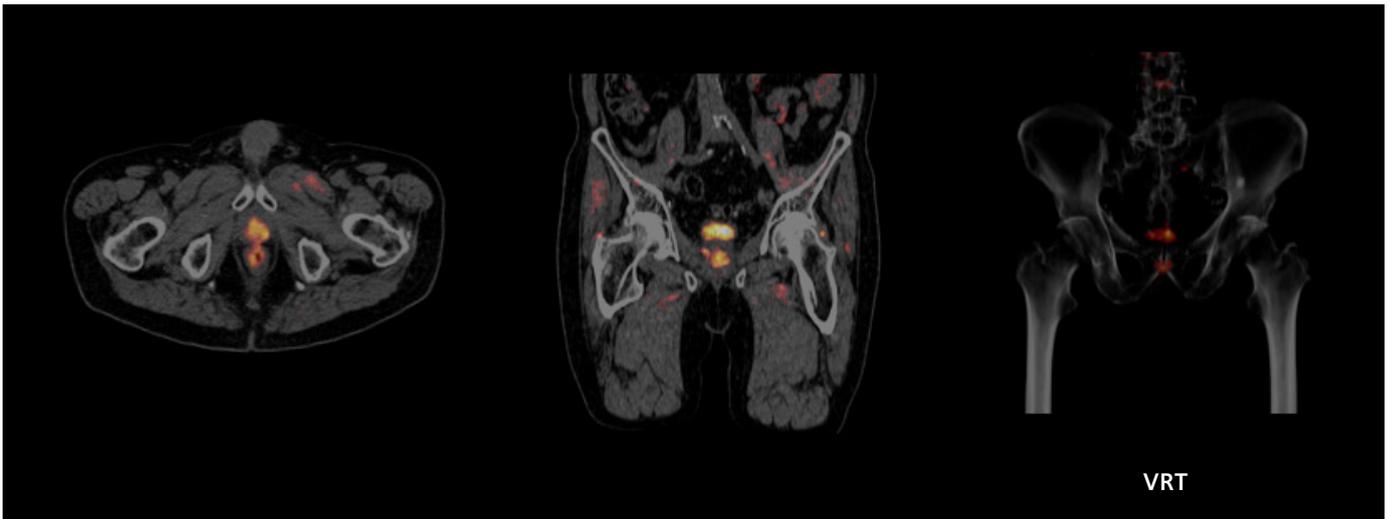
“Axumin fills the gap,” said Allis. “Once biochemical recurrence of prostate cancer is confirmed, based on sustained PSA levels, finding the site of recurrence with Axumin could facilitate appropriate patient management.”

FDA-approved prescribing information for Axumin (fluciclovine F 18) provides summaries from two clinical studies. Included is an evaluation of 105 images by three independent readers, each unaware of the clinical details of each patient or whether the biopsies of the prostate bed or suspicious lesions on imaging were positive or negative for cancer. On average, the readers correctly predicted the histology findings for 77 percent of the images (range: 75-79 percent). For the approximately one-third of images with suspicious lesions outside the region of the prostate bed, readers correctly identified the histology finding in an average of 90 percent of the images (range: 88-93 percent). The results seemed to be affected by PSA levels with, in general, lower PSA levels in patients with negative scans than in those with

positive scans. In patients with PSA levels ≤ 1.78 ng/mL, 15 of 25 had a positive scan, with 11 confirmed as positive by histology; 71 of 74 patients with PSA levels > 1.78 ng/mL had a positive scan, of which 58 were confirmed as positive.

Axumin is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure to patients and healthcare providers during administration. 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. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, is recommended.

The most commonly reported adverse reactions in patients are injection site pain, redness and a metallic taste in the mouth.



Moderate heterogenous prostate activity.
Biograph mCT 40
Parameters: 71 y/o male, 80 kg (176 lb)
Data courtesy of Blue Earth Diagnostics Ltd.

The right product, the right people

A viable radiopharmaceutical is not just about the drug itself. To ensure commercial access, with initial offerings in key U.S. markets, Blue Earth Diagnostics is working with Siemens' PETNET Solutions Inc., a wholly owned subsidiary of Siemens Medical Solutions USA, Inc., which will manufacture and act as the exclusive commercial supplier for Axumin in the U.S.

For Allis, the relationship is more than logistical: "Siemens' PETNET Solutions has a commitment and culture that can really make a difference for the patients. We believe that their focus and interest in PET will help maximize the potential of Axumin."

Barry Scott, head of Siemens' PETNET Solutions, clearly recognizes the importance of Axumin: "This is a big milestone. The PET industry has been waiting for new oncology biomarkers for years. Axumin is the first proprietary ^{18}F -labeled agent with an oncology indication approved by the FDA, and being

^{18}F -labeled enables efficient distribution. We are proud to work with Blue Earth Diagnostics as the exclusive commercial radiopharmaceutical supplier making Axumin available to imaging centers and their patients in the U.S."

Blue Earth Diagnostics is similarly focused. The company is patient-driven in its mission and led by recognized experts with decades of experience in the clinical development and commercialization of innovative molecular imaging products.

"There is a large unmet need in prostate cancer," said Allis. "And with a very experienced team and new, exciting products, it is incredibly rewarding for us to be charting new horizons that can benefit patient management decisions and advance the field of diagnostic PET imaging." ■

References

- ¹"Key statistics for prostate cancer." American Cancer Society. Accessed May 11, 2016. <http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics>
- ²"Understanding Prostate Cancer: Recurrence." Prostate Cancer Foundation. Accessed May 12, 2016. <http://www.pcf.org/site/c.1eJRIROePh/b.5822791/k.1DC2/Recurrence.htm>
- ³Choueiri et al. "A Model That Predicts the Probability of Positive Imaging in Prostate Cancer Case With Biochemical Failure After Initial Definitive Local Therapy." *The Journal of Urology*. March 2008. Vol. 179: 906-910. [http://www.jurology.com/article/S0022-5347\(07\)02834-0/fulltext](http://www.jurology.com/article/S0022-5347(07)02834-0/fulltext)

* Indications and important safety information for Axumin can be found on page 5. The full prescribing information can be found on pages 6-13.

Indication

Axumin™ (fluciclovine F 18) injection is 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.

Important Safety Information

- Image interpretation errors can occur with Axumin PET imaging. A negative image does not rule out recurrent prostate cancer and a positive image does not confirm its presence. The performance of Axumin seems to be affected by PSA levels. Axumin uptake may occur with other cancers and benign prostatic hypertrophy in primary prostate cancer. Clinical correlation, which may include histopathological evaluation, is recommended.
- Hypersensitivity reactions, including anaphylaxis, may occur in patients who receive Axumin. Emergency resuscitation equipment and personnel should be immediately available.
- Axumin use contributes to a patient's overall long-term cumulative radiation exposure, which is associated with an increased risk of cancer. Safe handling practices should be used to minimize radiation exposure to the patient and health care providers.
- Adverse reactions were reported in $\leq 1\%$ of subjects during clinical studies with Axumin. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.

To report suspected adverse reactions to Axumin, call 1-855-AXUMIN1 (1-855-298-6461) or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Full Axumin prescribing information is available on pages 6-13 and at: www.axumin.com

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AXUMIN safely and effectively. See [full prescribing information](#) for AXUMIN.

AXUMIN (fluciclovine F 18) injection, for intravenous use
Initial U.S. Approval: 2016

-----**INDICATIONS AND USAGE**-----

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 (1).

-----**DOSAGE AND ADMINISTRATION**-----

- Use appropriate radiation safety handling measures (2.1).
- Aseptically withdraw Axumin from its container and administer 370 MBq (10 mCi) as a bolus intravenous injection. (2.2).
- Initiate imaging 3-5 minutes after administration. Scanning should start from mid-thigh and proceed to base of skull, with a total scan time of approximately 20-30 minutes (2.4).
- The (radiation absorbed) effective dose associated with 370 MBq (10 mCi) of injected activity of Axumin is approximately 8 mSv (0.8 rem) in an adult (2.6).

-----**DOSAGE FORMS AND STRENGTHS**-----

Injection: clear, colorless solution in a 30 mL multiple-dose vial containing 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at calibration time and date (3).

-----**CONTRAINDICATIONS**-----

None (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Image interpretation errors can occur with Axumin imaging (5.1).
- Radiation risk: Axumin contributes to a patient’s long-term cumulative radiation exposure. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure (2.1, 5.3).

-----**ADVERSE REACTIONS**-----

Most commonly reported adverse reactions are injection site pain, erythema, and dysgeusia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Blue Earth Diagnostics, Ltd at 1-855-AXUMIN1 (1-855-298-6461) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for **PATIENT COUNSELING INFORMATION**

Revised: 5/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Axumin is indicated for positron emission tomography (PET) in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

Axumin is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration [see *Warnings and Precautions (5.3)*]. Use waterproof gloves and effective shielding, including syringe shields, when handling and administering Axumin.

2.2 Recommended Dose and Administration Instructions

The recommended dose is 370 MBq (10 mCi) administered as an intravenous bolus injection.

- Inspect Axumin visually for particulate matter and discoloration before administration. Do not use the drug if the solution contains particulate matter or is discolored.
- Use aseptic technique and radiation shielding when withdrawing and administering Axumin.
- Calculate the necessary volume to administer based on calibration time and date, using a suitably calibrated instrument. The recommended maximum volume of injection of undiluted Axumin is 5mL.
- Axumin may be diluted with Sodium Chloride Injection, 0.9%.
- After the Axumin injection, administer an intravenous flush of sterile Sodium Chloride Injection, 0.9% to ensure full delivery of the dose.
- Dispose of any unused drug in a safe manner in compliance with applicable regulations.

2.3 Patient Preparation Prior to PET Imaging

- Advise the patient to avoid any significant exercise for at least one day prior to PET imaging.
- Advise patients not to eat or drink for at least 4 hours (other than small amounts of water for taking medications) prior to administration of Axumin.

2.4 Image Acquisition Guidelines

Position the patient supine with arms above the head. Begin PET scanning 3 to 5 minutes after completion of the Axumin injection. It is recommended that image acquisition should start from mid-thigh and proceed to the base of the skull. Typical total scan time is between 20 to 30 minutes.

2.5 Image Display and Interpretation

Localization of prostate cancer recurrence in sites typical for prostate cancer recurrence is based on fluciclovine F 18 uptake in comparison with tissue background. For small lesions (less than 1cm in diameter) focal uptake greater than blood pool should be considered suspicious for prostate cancer recurrence. For larger lesions, uptake equal to or greater than bone marrow is considered suspicious for prostate cancer recurrence.

2.6 Radiation Dosimetry

The radiation absorbed doses estimated for adult patients following intravenous injection of Axumin are shown in Table 1. Values were calculated from human biodistribution data using OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential Modeling) software.

The (radiation absorbed) effective dose resulting from the administration of the recommended activity of 370 MBq of Axumin is 8 mSv. For an administered activity of 370 MBq (10 mCi), the highest-magnitude radiation doses are delivered to the pancreas, cardiac wall, and uterine wall: 38 mGy, 19 mGy, and 17 mGy, respectively. If a CT scan is simultaneously performed as part of the PET procedure, exposure to ionizing radiation will increase in an amount dependent on the settings used in the CT acquisition.

Table 1: Estimated Radiation Absorbed Doses in Various Organs/Tissues in Adults who Received Axumin

Organ/Tissue	Mean Absorbed Dose per Unit Administered Activity (microGy/MBq)
Adrenal glands	16
Brain	9
Breasts	14
Gallbladder wall	17
Lower large intestine wall	12
Small intestine wall	13
Stomach wall	14
Upper large intestine wall	13
Heart wall	52
Kidneys	14
Liver	33
Lungs	34
Muscle	11
Ovaries	13
Pancreas	102
Red bone marrow	25
Osteogenic cells	23
Skin	8
Spleen	24
Testes	17
Thymus gland	12
Thyroid	10
Urinary bladder wall	25
Uterus	45
Total body	13
Effective dose	22 (microSv/MBq)

3 DOSAGE FORMS AND STRENGTHS

Injection: supplied as a clear, colorless solution in a 30 mL multiple-dose vial containing 335 to 8200 MBq/mL (9 to 221 mCi/mL) fluciclovine F 18 at calibration time and date.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Image Misinterpretation

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. The performance of Axumin seems to be affected by PSA levels [See *Clinical Studies (14)*]. 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.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions including anaphylaxis may occur in patients who receive Axumin. Emergency resuscitation equipment and personnel should be immediately available.

5.3 Radiation Risks

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. Ensure safe handling to minimize radiation exposure to the patient and health care providers [see *Dosage and Administration (2.1)*].

6 ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The clinical trial database for Axumin includes data from 877 subjects including 797 males diagnosed with prostate cancer. 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 (range, 163 to 485 MBq).

Adverse reactions were reported in $\leq 1\%$ of subjects during clinical studies with Axumin. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Axumin is not indicated for use in females and there is no information on the risk of adverse development outcomes in pregnant women or animals with the use of fluciclovine F 18.

8.2 Lactation

Risk Summary

Axumin is not indicated for use in females and there is no information of the presence of fluciclovine F 18 in human milk.

8.3 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.4 Geriatric Use

Of the total number of patients in clinical studies of Axumin, the average age was 66 years with a range of 21 to 90 years. No overall differences in safety or effectiveness were observed between older subjects and younger subjects.

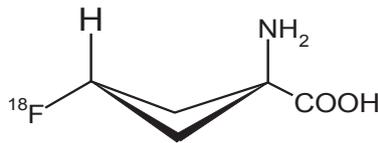
10 OVERDOSAGE

In case of overdose of Axumin, encourage patients to maintain hydration and to void frequently to minimize radiation exposure.

11 DESCRIPTION

11.1 Chemical Characteristics

Axumin contains the fluorine 18 (F 18) labeled synthetic amino acid analog fluciclovine. Fluciclovine F 18 is a radioactive diagnostic agent used with PET imaging. Chemically, fluciclovine F 18 is (1r, 3r)-1-amino-3-[¹⁸F]fluorocyclobutane-1-carboxylic acid. The molecular weight is 132.1 and the structural formula is:



Axumin is a sterile, non-pyrogenic, clear, colorless, hyperosmolal (approximately 500 - 540 mOsm/kg) injection for intravenous use. Each milliliter contains up to 2 micrograms of fluciclovine, 335 to 8200 MBq (9 to 221 mCi) fluciclovine F 18 at calibration time and date, and 20 mg trisodium citrate in water for injection. The solution also contains hydrochloric acid, sodium hydroxide and has a pH between 4 and 6.

11.2 Physical Characteristics

Fluorine 18 (F 18) is a cyclotron produced radionuclide that decays by positron emission (β^+ decay, 96.7%) and orbital electron capture (3.3%) to stable oxygen 18 with a physical half-life of 109.7 minutes. The positron can undergo annihilation with an electron to produce two gamma rays; the energy of each gamma ray is 511 keV (Table 3).

Table 2: Principal Radiation Produced from Decay of Fluorine 18 Radiation

	Energy (keV)	Abundance (%)
Positron	249.8	96.7
Gamma	511.0	193.5

11.3 External Radiation

The point source air-kerma coefficient for F 18 is 3.75×10^{-17} Gy m²/(Bq s). The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by F 18 that results from various thicknesses of lead shielding is shown in Table 4. The use of 8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.

Table 3: Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shield Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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.

12.3 Pharmacokinetics

Distribution

Following intravenous administration, fluciclovine F 18 distributes to the liver (14% of administered activity), pancreas (3%), lung (7%), red bone marrow (12%) and myocardium (4%). With increasing time, fluciclovine F 18 distributes to skeletal muscle.

Excretion

Across the first four hours post-injection, 3% of administered radioactivity was excreted in the urine. Across the first 24 hours post-injection, 5% of administered radioactivity was excreted in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long term studies in animals have been performed to evaluate the carcinogenic potential of fluciclovine.

Mutagenesis

Fluciclovine was not mutagenic *in vitro* in reverse mutation assay in bacterial cells and in chromosome aberration test in cultured mammalian cells, and was negative in an *in vivo* clastogenicity assay in rats after intravenous injection of doses up to 43 mcg/kg. However, fluciclovine F 18 has the potential to be mutagenic because of the F 18 radioisotope.

Impairment of Fertility

No studies in animals have been performed to evaluate potential impairment of fertility in males or females.

14 CLINICAL STUDIES

The safety and efficacy of Axumin were evaluated in two studies (Study 1 and Study 2) in men with suspected recurrence of prostate cancer based on rising PSA levels following radical prostatectomy and/or radiotherapy.

Study 1 evaluated 105 Axumin scans in comparison to histopathology obtained by biopsy of the prostate bed and biopsies of lesions suspicious by imaging. PET/CT imaging generally included the abdomen and pelvic regions. The Axumin images were originally read by on-site readers. The images were subsequently read by three blinded independent readers. Table 4 shows the performance of Axumin in the detection of recurrence in each patient scan and, specifically, within the prostatic bed and extra-prostatic regions, respectively. The results of the independent read were generally consistent with one another and confirmed the results of the on-site reads.

Table 4: Performance of Axumin in Patients with Biochemically Suspected Recurrent Prostate Cancer, at the Patient Level and at the Prostate Bed and Extraprostatic Region 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 detection rate of Axumin seems to be affected by PSA levels [see *Warnings and Precautions (5.1)*]. In general, patients with negative scans had lower PSA values than those with positive scans. The detection rate (number with positive scans/total scanned) for patients with a PSA value of less than or equal to 1.78 ng/mL (1st PSA quartile) was 15/25, of which 11 were histologically confirmed as positive. In the remaining three PSA quartiles, the detection rate was 71/74, of which 58 were histologically confirmed. Among the 25 patients in the first PSA quartile, there were 4 false positive scans and 1 false negative scan. For the 74 patients with PSA levels greater than 1.78 ng/mL, there were 13 false positive scans and no false negative scans.

Study 2 evaluated the concordance between 96 Axumin and C11 choline scans in patients with median PSA value of 1.44 ng/mL (interquartile range = 0.78 to 2.8 ng/mL). The C 11 choline scans were read by on-site readers. The Axumin scans were read by the same three blinded independent readers used for Study 1. The agreement values between the Axumin and C11 choline reads were 61%, 67% and 77%, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Axumin is supplied as a clear, colorless injection in a 30 mL multiple-dose glass vial containing approximately 26 mL solution of 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at calibration time and date.

30 mL sterile multiple-dose vial: NDC 69932-001-030

16.2 Storage and Handling

Store Axumin at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Axumin does not contain a preservative. Store Axumin within the original container in radiation shielding.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

17 PATIENT COUNSELING INFORMATION

- Instruct patients to avoid significant exercise for at least a day before the PET scan.
- Instruct patients not to eat or drink for at least 4 hours before the PET scan (other than small amounts of water for taking medications).

Marketed by Blue Earth Diagnostics Ltd. Oxford, UK OX4 4GA

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