White paper

A novel option for the diagnosis of biochemical recurrence of prostate cancer

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Executive summary

The timely detection and localization of lesions in patients with biochemical recurrence (BCR) of prostate cancer is clinically challenging and crucial for the further management of these patients. Positron emission tomography/computed tomography (PET/CT) using radiolabeled amino acids such as Axumin® (fluciclovine F 18) injection* shows very encouraging results in the localization of prostate cancer recurrence in the prostate/ prostate bed, lymph nodes, and bone. The relatively long half-life and favorable biodistribution of Axumin have the potential to facilitate its broad clinical adoption for PET/CT imaging in patients with BCR of prostate cancer. Clinical data highlight its potential to provide clinically useful information that may impact patient management. Based on Axumin's safety and efficacy results in two clinical studies, the US Food and Drug Administration (FDA) granted approval in 2016 and the European Medicines Agency granted approval in 2017, for PET imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment. In addition, the regional Medicare Administrative Contractors throughout the US have provided coverage for Axumin PET/CT imaging for patients with BCR of prostate cancer since early 2017.

*Axumin® (fluciclovine F 18) injection

Indication and usage

Axumin® (fluciclovine F 18) injection 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.

Important Safety Information

- Image interpretation errors can occur with fluciclovine PET imaging. A negative image does not rule out recurrent prostate cancer and a positive image does not confirm its presence.
- The performance of fluciclovine seems to be affected by PSA levels. Fluciclovine 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 fluciclovine. 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 ≤1% of subjects during clinical studies with fluciclovine. 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.

Please see full prescribing information at www.axumin.com or pages 19-26.

Fludeoxyglucose F18 5-10mCi as an IV injection

*Indications and usage

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- Oncology: For assessment of 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 diagnosis of cancer.
- Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

Important Safety Information

- Radiation Risks: Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker.
- Blood Glucose Abnormalities: In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.
- Adverse Reactions: Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available. Full prescribing information for Fludeoxyglucose F 18 Injection can be found at the conclusion of this publication.

Dosage forms and strengths

Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanolas a stabilizer (approximately 15 to 50 mL volume) for intravenous administration. Fludeoxyglucose F 18 injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

[a] For indications and important safety information for Fludeoxyglucose F 18 injection (^{18}F FDG) see page 4.
For full prescribing information see pages 27-38.

Sodium Fluoride F 18 Injection for Intravenous Use

*Indications and usage

Sodium fluoride F 18 injection (10–200 mCi/mL) is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging bone to define areas of altered osteogenic activity.

Important Safety Information

- Allergic Reactions: As with any injectable drug, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.
- Cancer Risk: Sodium fluoride F 18 injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and healthcare worker.
- Adverse Reactions: No adverse reactions have been reported based on a review of the published literature, publicly available reference sources and adverse drug reaction reporting systems. The completeness of the sources is not known.

Dosage Forms and Strengths

Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) at EOS reference time of no-carrier-added sodium fluoride F18 in aqueous 0.9% sodium chloride solution. Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration. Sodium Fluoride F 18 Injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

For full prescribing information see pages 39-46.

Introduction

Prostate cancer represents 9.6% of all new cancer cases in the US[1]. It occurs only in men, with increasing incidence with age, in African American men as well as those with a family history are at higher risk. In 2017, circa 161,360 new cases of prostate cancer were diagnosed and approximately 26,730 men succumbed to the disease[1]. Prostate cancer may be cured when localized, but up to one-third of patients who undergo radical prostatectomy or radiotherapy (RT) for clinically localized prostate cancer will develop a BCR within 10 years of the primary treatment[2]. BCR of prostate cancer is defined by elevated PSA levels, which may occur years before the recurrence is defined. The identification and localization of recurrent tumors is of utmost importance to provide clinicians and patients with additional guidance when making management plans*.

PET/CT is a imaging technique to detect subtle biochemical changes within the human body, which often precede anatomical abnormalities detectable by a CT scan alone. PET detects abnormal accumulation of radiolabeled biomolecules (known as PET tracers) *in vivo*. Those molecules are relevant to cellular processes, such as glucose-, amino acid-, and fatty acid metabolism, which are often increased in malignant cells[3]. While the radiolabeled glucose analog Fludeoxyglucose F 18 (FDG) injection** is the most common PET tracer in clinical practice, its usefulness in prostate cancer is limited to specific subgroups of patients. In addition to diagnosis and staging of primary tumors with a high Gleason score (GS), it shows promising results in the assessment of the extent of active castrate-resistant disease, in monitoring response to therapies, and in prognostication. FDG PET/CT seems to be able to detect metastatic disease in only a fraction of men with BCR; its sensitivity increases with increasing PSA level[4].

FDG was compared with an alternative tracer, carbon-11 (C 11)-radiolabeled choline, as part of a dual tracer study of detection of BCR in 73 men with recurrence after initial therapy[5]. The authors reported that although C 11 choline appeared to be more sensitive than FDG for the detection of BCR, FDG was better at discriminating the proliferative character of the disease.5 In 2012, C 11 choline was approved by the US FDA to investigate patients with elevated blood PSA levels after prior treatment for prostate cancer[6]. Due to the short half-life of C 11 (20 minutes), the use of C 11 choline is limited to PET/CT centers with an on-site cyclotron. A further limitation of C 11 choline PET/CT, a dependence on the PSA level and other PSA kinetics, has been discussed by several authors – with a lower prostate cancer detection rate in patients with low PSA levels or a PSA doubling time (PSA DT) of more than six months[7, 8].

Other classes of radiotracers such as fatty acid analogs, newer-generation prostate-specific membrane antigen ligands, and cell membrane analogs labeled with different positron emitters other than C 11, are all under investigation in the BCR setting, with Sodium Fluoride F 18 (NaF) injection*** showing good sensitivity and specificity for detecting recurrence in bone.9 Moreover, the amino acid analog Axumin (fluciclovine F 18) injection was approved in 2016 in the setting of BCR and its diagnostic performance has been recently summarized[10, 11].The safety profile for these products is essentially comparable.

*Axumin is not currently approved for use in patient management decisions.

Axumin (fluciclovine F 18) injection: general information

As in many neoplasms, amino acid transport is upregulated in prostate cancer in order to address the cell's increased amino acid demand for energy requirements and protein synthesis. The use of radiolabeled amino acids for PET/CT of prostate cancer can be an attractive alternative to PET/CT with commonly used FDG, particularly given that FDG uptake is closely tied to glucose metabolism[12, 13].

Axumin is a synthetic, amino acid analog PET agent, which is taken up into prostate cancer cells via amino acid transporters, but is not metabolized nor incorporated into proteins. Axumin was approved by the FDA in May 2016 and is indicated "for PET imaging in men with suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following prior treatment[14, 15]."

Blue Earth Diagnostics Ltd. is the NDA holder and owner of Axumin. It is commercialized in the US by its subsidiary, Blue Earth Diagnostics, Inc., and is manufactured and distributed by PETNET Solutions Inc., a Siemens Healthineers company.

Dosage and acquisition

The Axumin imaging protocol is as follows: 370 MBq (10 mCi) of Axumin is injected intravenously into the patient and the PET acquisition is begun 3 to 5 minutes later. The patient should not eat or drink for at least 4 hours before administration, and should avoid any significant exercise for at least a day prior to injection. Image acquisition starts from mid-thigh and proceeds to the base of the skull with an expected typical scan time of 20–30 minutes because of the typical efflux of the tracer from the tumor over time[16].Urinary excretion is typically delayed so there is usually limited activity in the bladder during the imaging window.

The effective dose resulting from the administration of the recommended activity of Axumin is 8 mSv, with the highest radiation doses in the pancreas, cardiac wall, and uterine wall[15].

Mechanism of action

Of the several amino acid transporters that are overexpressed in prostate cancer, system L amino acid transporter1 (LAT1) and system alanine-serine-cysteine transporter2 (ASCT2) play an important role in Axumin transport[17].The expression of LAT1 in prostate cancer is correlated with Gleason Score[18] and initial data suggest that, as a tumor progresses into castration resistance, LAT1 transport of Axumin becomes more active[16]. Also, the expression of ASCT2 is linked with more aggressive types of prostate cancer and is also susceptible to stimulation by androgen signaling in androgen-dependent prostate cancer[19, 20].

As discussed above, PSA level, PSA DT, and GS can be influential in the detection of prostate cancer by various imaging procedures. The detection rate of prostate cancer with Axumin increases with higher PSA levels[21].

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Normal distribution

As with any radiopharmaceutical, Axumin has a characteristic physiological tissue uptake pattern that can vary among patients and which could lead to false positive or negative findings, especially if the expected distribution and uptake patterns are not fully understood and anticipated. After reviewing Axumin uptake patterns from 611 imaging procedures from 16 clinical trials involving six centers – including dosimetry studies on 12 healthy volunteers – Schuster et al. concluded that common physiologic uptake patterns in patients were similar to those in healthy volunteers[16]. The distribution of the tracer reflected the presence of amino acid transport and metabolism with the highest intensity in the pancreas and liver. There was a moderate heterogeneous marrow activity, which decreased over time, and the authors also described mild muscle activity which increased with time. Moderate accumulation was seen in salivary glands, lymphoid, and pituitary tissue, whereas variable mild to moderate activity was present in the bowel and the kidneys with minimal renal excretion and bladder uptake. The latter combined with the lack of significant brain uptake underline the potential of Axumin for pelvic and brain imaging, respectively.

Incidental findings

In addition to prostate cancer, Axumin uptake has been reported in breast, lung, and colon cancer, as well as squamous cell carcinoma of the scalp, some hematologic malignancies, and in primary and metastatic brain tumors*[16].

The tracer uptake in renal malignancies depends on the histology, and as with other tracers any degree of Axumin accumulation in a renal mass can be of malignant origin. Due to the intense liver uptake, benign liver lesions are photopenic compared with healthy liver tissue[16].

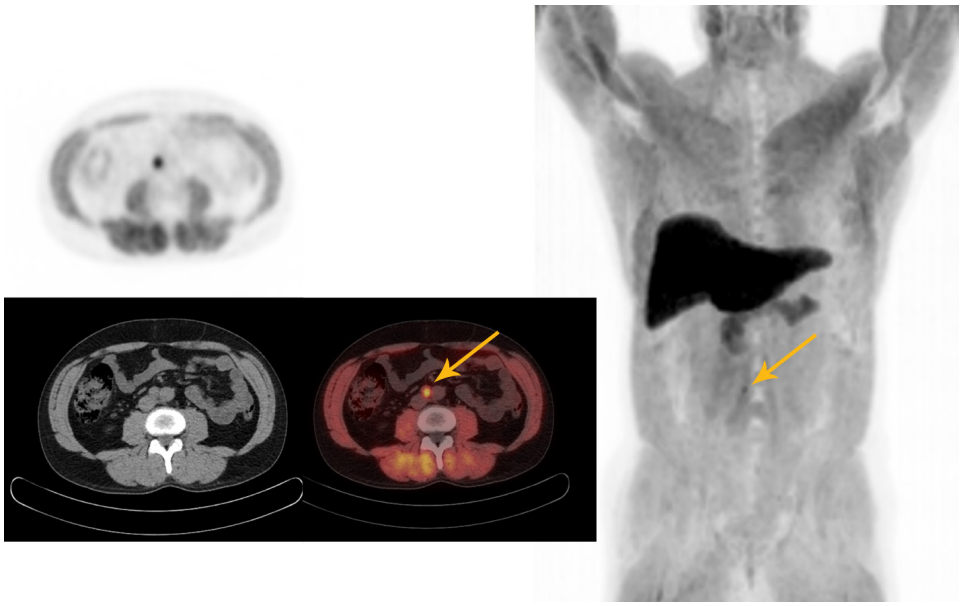
As a non-specific radiotracer, Axumin can accumulate in areas of acute and chronic infection, as well as inflammation, and in benign neoplasms such as meningioma[16]. This necessitates careful correlation with the clinical assessment and the coregistered CT images.

*Axumin® (fluciclovine F 18) injection 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.

Axumin and prostate cancer

Axumin and prostate cancer recurrence

As discussed above, the current US regulatory approval for Axumin is for patients with "suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment[14]."



Case study 1: Patient after prostatectomy, now PSA of 0.4 ng/ml and a doubling time of 3 months. All conventional images were stable and did not show any sign of malignancy. Patient was scheduled for excisional biopsy. The Axumin PET/CT identified a single para aortic lymph node suspicious for prostate cancer. Images courtesy of Bital Savir-Baruch, MD, Loyola University Medical Center, Maywood, IL.

Diagnostic performance

The clinical data supporting FDA approval can be found in the clinical studies (Section 14) of the Axumin full prescribing information on page 19. These data from 2 clinical studies[25, 26], along with those from a compassionate use program in Norway, were pooled in a retrospective study of the diagnostic performance of Axumin in subjects with BCR of prostate cancer (NCT02443571)[10]. In total, 596 patients across the 4 study sites underwent Axumin PET/CT scanning. Histological data were available as a truth standard to confirm the Axumin findings for 143 of the scans.

The overall subject level detection rate was 68%, with positive findings detected in the prostate/bed, pelvic lymph node, and extrapelvic regions in 39%, 33%, and 26% of scans, respectively. Skeletal involvement was revealed in 9% (55/610) of cases, despite a requirement by one of the contributing studies25 that subjects had a negative conventional bone scan prior to enrollment. Extra nodal soft tissue lesions were very rare and seen in less than 1% of cases. The positive predictive value (PPV) of Axumin PET/CT for extraprostatic involvement was 92% (36/39; 95% CI: 79–98), for prostate/bed disease was 72% (74/103; 95% CI: 62–80), while the lesion-level analysis, was 62% (153/246; 95% CI: 56–68)[10].

A correlation was observed between PSA levels and the detection rate for local recurrence and extraprostatic metastases (Figure 1), with a subject-level detection rate of over 40% in the lowest PSA quartile (≤ 0.79 ng/mL).

In a prospective study of 89 patients, Nanni et al. reported a diagnostic accuracy of 38% for Axumin, with a sensitivity of 37%, a specificity of 67%, a PPV of 97% and a negative predictive value of 4%[11]. Importantly, among those with a baseline PSA <1 ng/mL, the sensitivity of C 11 choline was 21%[11].

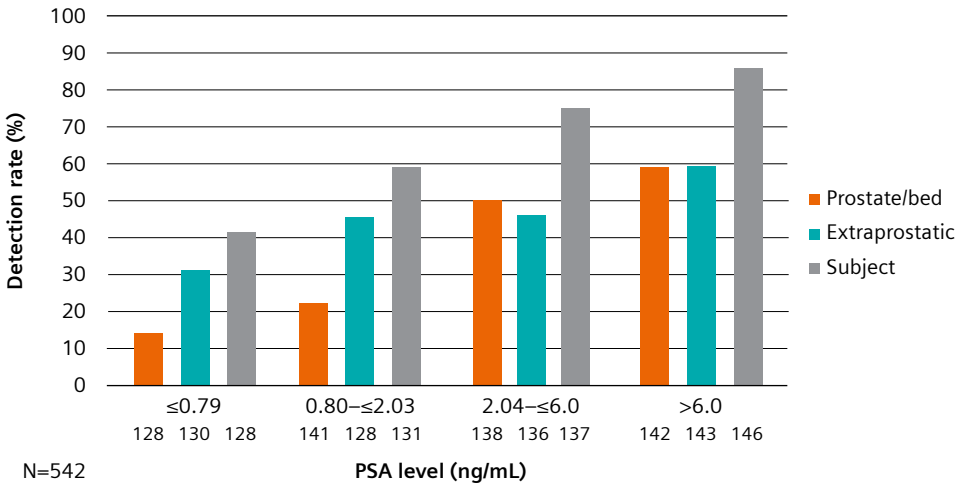


Figure 1: Axumin detection rate by PSA quartile[10]. (adapted from Bach-Gansmo, 2017)

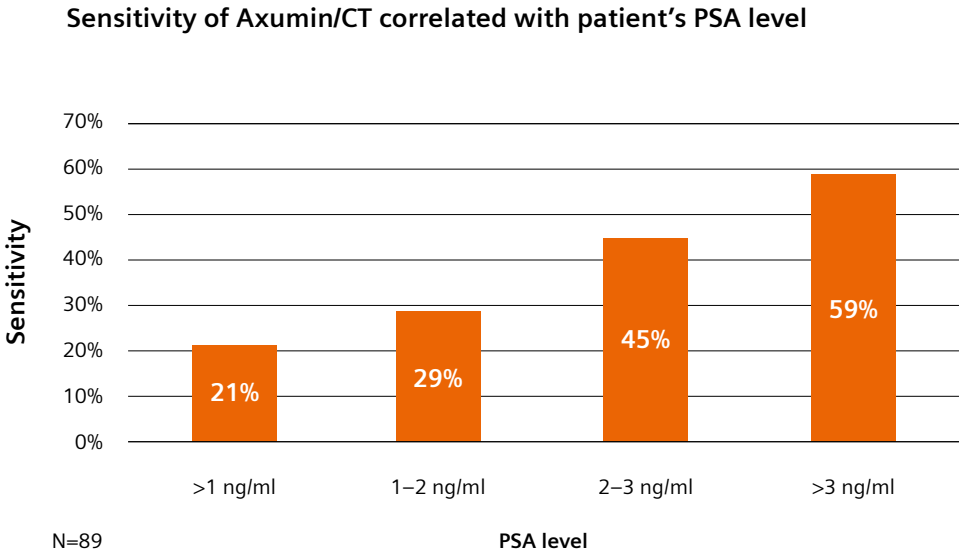
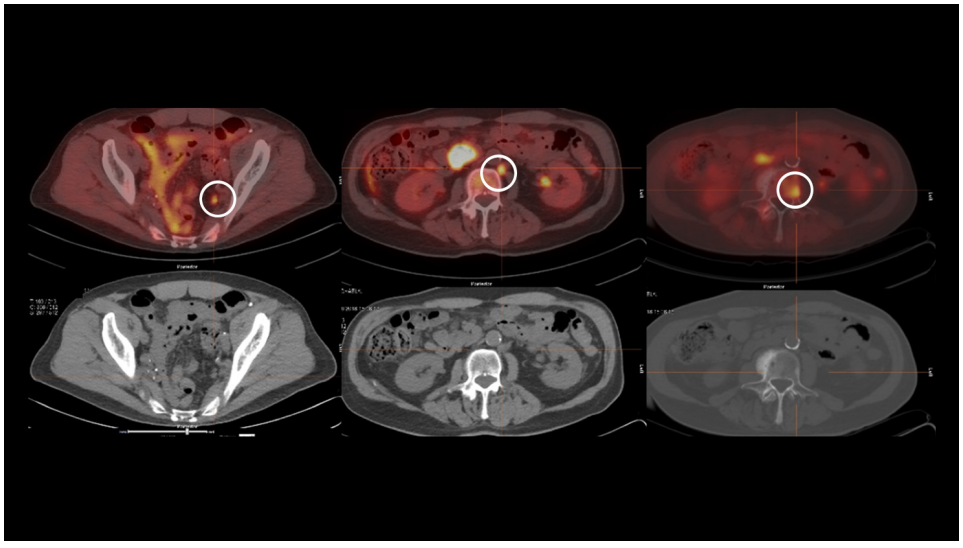


Figure 2: Sensitivity of Axumin PET/CT for different PSA levels, (adapted from Nanni, 2016).



Case study 2: Patient with low-risk prostate adenocarcinoma (Gleason score 3+3, external radiotherapy completed in 2008). Nadir PSA 1.7 with PSA of 26 ng/ml in 2016. CT and Bone scintigram were both negative, a local prostate biopsy was positive. PET/CT results showed lymph node involvement and skeletal metastases. Images courtesy of Bital Savir-Baruch, MD, Loyola University Medical Center, Maywood, IL.

Ongoing research with ^{18}F fluciclovine

Salvage RT represents a viable treatment option for patients with BCR of prostate cancer after radical prostatectomy. Current challenges with respect to target volumes definition and delivered dose include the effect of microscopic versus macroscopic disease on the effective dose to achieve biochemical control. The differentiation between a local and a locoregional relapse will impact decisions regarding the appropriate extent of the RT[27]. Therefore, the utility of ^{18}F fluciclovine PET/CT to define the site and extent of the recurrent cancer and to facilitate appropriate patient management is of great interest.

Encouraged by case reports, Akin-Akintayo et al. initiated a prospective, randomized clinical trial and reported on an initial 87 patients with BCR of prostate cancer[28]. Forty-four of the 87 patients were randomly selected to undergo a ^{18}F fluciclovine PET/CT study prior to finalization of the RT management plan. The RT plan decisions before and after the ^{18}F fluciclovine PET/CT were compared in 42 patients after 2 patients dropped out of the trial. In total, 34 of the 42 patients had positive findings in the ^{18}F fluciclovine PET/CT, which led to a change in the planned RT in 17 of the 42 patients (Table 1).

The clinical impact of ^{18}F fluciclovine PET/CT on therapeutic management decisions for men with BCR of prostate cancer following primary treatment is further being investigated in 2 prospective, open-label Phase III multisite trials. FALCON (NCT02578940) and LOCATE (NCT02680041) are currently underway in the UK and the US, respectively, evaluating subjects who are being considered for salvage treatment with curative intent. FALCON compared a subject's intended management plan as recorded prior to ^{18}F fluciclovine PET/CT imaging with the plan post-scan. The trial recently terminated recruitment early and interim data from the first 85 evaluable patients in FALCON show that patient management was revised post-scan in 52/85 (61%) patients[29]. Initial safety data appear consistent with those summarized in the US prescribing information. LOCATE also recently completed enrollment and results are anticipated in 2018.

Figure 3: Impact of Axumin on RT plans for patients with BCR of prostate cancer[28]. (adapted from Akin Akintoyo, 2017)

	N (%)
Number of patients undergoing Axumin PET/CT	42 (100%)
Number of patients with positive findings in PET/CT	34 (81%)
Number of patients with changed RT plan	17 (40%)

Other imaging agents

A number of other imaging modalities are utilized in the setting of BCR of prostate cancer and have been evaluated in various studies.

a) Choline

A summary of the studies that supported the FDA approval for C11 Choline are included in the full prescribing information for C11 Choline.

In a prospective study of 89 patients, Nanni et al. reported a diagnostic accuracy of 32% for C 11 choline with a sensitivity of 32%, specificity of 40%, PPV of 90% and a negative predictive value of 3%.11 Furthermore, among those with a baseline PSA <1 ng/mL, the sensitivity of C 11 choline was 14%[11].

b) CT

Utility of CT for detecting BCR after radical prostatectomy is limited – with one study reporting that only 11% of patients will show a positive CT result[30] and another a study of 132 men with BCR after radical prostatectomy reporting the mean PSA level associated with a positive CT result to be 27.4 ng/mL[31].

Odewole et al. conducted a retrospective analysis of 53 patients with negative bone scans, but suspected BCR of prostate cancer, who underwent routine CT imaging[21]. They reported the accuracy of CT in the prostate/bed region to be 35% (n=42), with an accuracy of 44% in the extraprostatic region (n=41).

Investigational agents in BCR imaging

A number of studies are underway with PSMA-based investigational agents, Ga 68 PSMA and F 18 PSMA. In addition to being FDA-approved, Axumin offers a number of positive technical attributes, including a favorable synthesis method, appropriate half-life and the ability to distribute easily using existing fluorodeoxyglucose transport networks[32, 33].

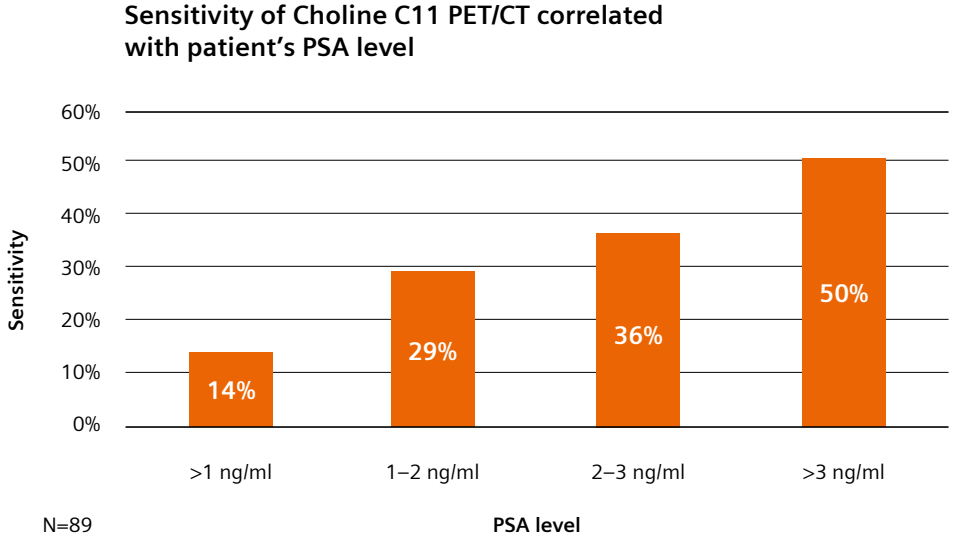


Figure 4: Sensitivity of Choline C11 PET/CT for different PSA levels, (adapted from Nanni, 2016).

Reimbursement in the US

As of January 1, 2017, all of the regional Medicare Administrative Contractors throughout the US have agreed to provide coverage for Axumin imaging in men with elevated PSA levels following definitive therapy for prostate cancer.

Axumin also has a product-specific Healthcare Common Procedure Coding System (HCPCS) Code (an "A Code") effective January 1, 2017. For claims with dates of service on or after that date, the following HCPCS code should be used: A9588 Fluciclovine F 18, diagnostic, 1 mCi.

Axumin's transitional pass-through payment status for Medicare patient scans performed in the hospital outpatient department ended on January 1, 2020. Payment by many private insurers is still evolving, and Blue Earth Diagnostics is working with physicians who are interested in advocating for Axumin coverage with radiology benefit managers and private insurers regarding coverage and payment for the appropriate use of Axumin.

Conclusion

The optimal management of patients with BCR of prostate cancer depends on early and accurate localization of lesions. Axumin PET/CT is FDA-approved in this setting where it has been established to have a good diagnostic performance for local and extraprostatic lesions across a varying range of PSA levels. A stable half-life and favourable biodistribution profile further highlight its potential for clinical use. The safety profile for these products is essentially comparable.

Glossary

PSA: Prostate-specific antigen

PC: Prostate cancer

PET: Positron emission tomography

CT: Computed tomography

FACBC F18: Anti-1-amino-3-^{18}F-fluorocyclobutane- 1-carboxylic acid (= Fluciclovine)

LAT1: L amino acid transporter1

ASCT2: system alanine-serine-cysteine transporter2

FDG: Fluodeoxyglucose F 18

PSA DT: PSA Doubling Time

GS: Gleason score

SUV: Standard uptake value

BPH: Benign prostate hyperplasia

MRI: Magnetic resonance imaging

TP: True positives

TN: True negatives

FP: False positives

FN: False negatives

SPECT: Single photon emission computed tomography

SRT: Salvage radiotherapy

MAC: Medicare Administrative Contractors

HCPCS: Healthcare Common Procedure Coding System.

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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: 8/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 ≤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.

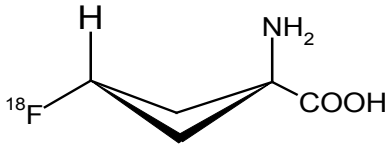
10 OVERDOSAGE

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[^{18}F]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 (ß+ 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 2).

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 x 10^{-17} Gy m^2/(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 3. 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 than1.78 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 69932-001-30

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).

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Axumin™ is a trademark of Blue Earth Diagnostics Ltd.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Fludeoxyglucose F 18 Injection safely and effectively. See full prescribing information for Fludeoxyglucose F 18 Injection.

Fludeoxyglucose F 18 Injection, USP
For intravenous use
Initial U.S. Approval: 2005

----------INDICATIONS AND USAGE----------
Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- Oncology: For assessment of 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 diagnosis of cancer.
- Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures (1).

----------DOSAGE AND ADMINISTRATION----------
Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

- In the oncology and neurology settings, instruct patients to fast for 4 to 6 hours prior to the drug's injection**.** Consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to the drug's administration (5.2).
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection facilitates localization of cardiac ischemia (2.3).

Aseptically withdraw Fludeoxyglucose F 18 Injection from its container and administer by intravenous injection (2).
The recommended dose:

- for adults is 5 to 10 mCi (185 to 370 MBq), in all indicated clinical settings (2.1).
- for pediatric patients is 2.6 mCi (96.2 MBq) in the neurology setting (2.2).

Initiate imaging within 40 minutes following drug injection; acquire static emission images 30 to 100 minutes from time of injection (2).

----------DOSAGE FORMS AND STRENGTHS----------
Multi-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration (3).

----------CONTRAINDICATIONS----------
None.

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

- Radiation risks: use smallest dose necessary for imaging (5.1).
- Blood glucose abnormalities: may cause suboptimal imaging (5.2).

----------ADVERSE REACTIONS----------
Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available (6).

To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for 9 hours after Fludeoxyglucose F 18 Injection (8.2).
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

1.1 Oncology

For assessment of 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 diagnosis of cancer.

1.2 Cardiology

For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

1.3 Neurology

For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

2 DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [*see Description (11.2)*].

2.1 Recommended Dose for Adults

Within the oncology, cardiology and neurology settings, the recommended dose for adults is 5 to 10 mCi (185 to 370 MBq) as an intravenous injection.

2.2 Recommended Dose for Pediatric Patients

Within the neurology setting, the recommended dose for pediatric patients is 2.6 mCi, as an intravenous injection. The optimal dose adjustment on the basis of body size or weight has not been determined [*see Use in Special Populations (8.4)*].

2.3 Patient Preparation

- To minimize the radiation absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [*see Warnings and Precautions (5.2)*]. Prior to Fludeoxyglucose F 18 PET imaging in the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug's injection.

- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F 18 Injection facilitates localization of cardiac ischemia.

2.4 Radiation Dosimetry

The estimated human absorbed radiation doses (rem/mCi) to a newborn (3.4 kg), 1-year old (9.8 kg), 5-year old (19 kg), 10-year old (32 kg), 15-year old (57 kg), and adult (70 kg) from intravenous administration of Fludeoxyglucose F 18 Injection are shown in Table 1. These estimates were calculated based on human[2] data and using the data published by the International Commission on Radiological Protection[4] for Fludeoxyglucose ^{18}F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated are the urinary bladder, heart, pancreas, spleen, and lungs.

Table 1. Estimated Absorbed Radiation Doses (rem/mCi) After Intravenous Administration of Fludeoxyglucose F 18 Injection[a]

Organ	Newborn (3.4 kg)	1-year old (9.8 kg)	5-year old (19 kg)	10-year old (32 kg)	15-year old (57 kg)	Adult (70 kg)
Bladder wall[b]	4.3	1.7	0.93	0.60	0.40	0.32
Heart wall	2.4	1.2	0.70	0.44	0.29	0.22
Pancreas	2.2	0.68	0.33	0.25	0.13	0.096
Spleen	2.2	0.84	0.46	0.29	0.19	0.14
Lungs	0.96	0.38	0.20	0.13	0.092	0.064
Kidneys	0.81	0.34	0.19	0.13	0.089	0.074
Ovaries	0.80	0.8	0.19	0.11	0.058	0.053
Uterus	0.79	0.35	0.19	0.12	0.076	0.062
LLI wall *	0.69	0.28	0.15	0.097	0.060	0.051
Liver	0.69	0.31	0.17	0.11	0.076	0.058
Gallbladder wall	0.69	0.26	0.14	0.093	0.059	0.049
Small intestine	0.68	0.29	0.15	0.096	0.060	0.047
ULI wall **	0.67	0.27	0.15	0.090	0.057	0.046
Stomach wall	0.65	0.27	0.14	0.089	0.057	0.047
Adrenals	0.65	0.28	0.15	0.095	0.061	0.048
Testes	0.64	0.27	0.14	0.085	0.052	0.041
Red marrow	0.62	0.26	0.14	0.089	0.057	0.047
Thymus	0.61	0.26	0.14	0.086	0.056	0.044
Thyroid	0.61	0.26	0.13	0.080	0.049	0.039
Muscle	0.58	0.25	0.13	0.078	0.049	0.039
Bone surface	0.57	0.24	0.12	0.079	0.052	0.041
Breast	0.54	0.22	0.11	0.068	0.043	0.034
Skin	0.49	0.20	0.10	0.060	0.037	0.030
Brain	0.29	0.13	0.09	0.078	0.072	0.070
Other tissues	0.59	0.25	0.13	0.083	0.052	0.042

[a] MIRDOSE 2 software was used to calculate the radiation absorbed dose.
[b] The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.
*LLI = lower large intestine; **ULI = upper large intestine

2.5 Radiation Safety – Drug Handling

- Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F 18 Injection to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [*see Description (11.2)*].
- The dose of Fludeoxyglucose F 18 used in a given patient should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.

2.6 Drug Preparation and Administration

- Calculate the necessary volume to administer based on calibration time and dose.
- Aseptically withdraw Fludeoxyglucose F 18 Injection from its container.
- Inspect Fludeoxyglucose F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer the drug if it contains particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

2.7 Imaging Guidelines

- Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
- Acquire static emission images 30 to 100 minutes from the time of injection.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [*see Dosage and Administration (2.5)*].

5.2 Blood Glucose Abnormalities

In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

6 ADVERSE REACTIONS

Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting. Have emergency resuscitation equipment and personnel immediately available.

7 DRUG INTERACTIONS

The interactions of Fludeoxyglucose F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from published case series and case reports describe Fludeoxyglucose F 18 Injection crossing the placenta with uptake by the fetus (see Data). All radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. However, published studies that describe Fludeoxyglucose F 18 Injection use in pregnant women have not identified a risk of drug-associated major birth defects, miscarriage, or adverse maternal or fetal outcomes. If considering Fludeoxyglucose F 18 Injection administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from Fludeoxyglucose F 18 Injection and the gestational timing of exposure.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Human Data

Data from published case series and case reports describe Fludeoxyglucose F 18 Injection crossing the placental barrier and visualization of radioactivity throughout the body of the fetus. The estimated fetal absorbed radiation dose from the maximum

labeled dose (370 MBq) of Fludeoxyglucose F 18 was 10 mGy with first trimester exposure to PET alone and 20 mGy with first trimester exposure to PET/CT scan combination. Long-term adverse radiation effects to a child exposed to Fludeoyxglucose F 18 Injection in utero are unknown. No adverse fetal effects or radiation-related risks have been identified for diagnostic procedures involving less than 50 mGy, which represents less than 20 mGy fetal doses.

8.2 Lactation

Risk Summary

A published case report and case series show the presence of Fludeoxyglucose F 18 Injection in human milk following administration. There are no data on the effects of Fludeoxyglucose F 18 Injection on the breastfed infant or the effects on milk production. Exposure of Fludeoxyglucose F 18 Injection to a breastfed infant can be minimized by temporary discontinuation of breastfeeding (see Clinical Considerations). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fludeoxyglucose F 18 Injection, any potential adverse effects on the breastfed child from Fludeoxyglucose F 18 Injection or from the underlying maternal condition.

Clinical Considerations

To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breastmilk and avoid close (breast) contact with the infant for at least 9 hours after the administration of Fludeoxyglucose F 18 Injection.

8.4 Pediatric Use

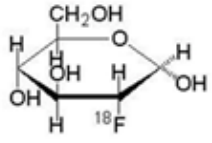
The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined.

In the oncology or cardiology settings, the safety and effectiveness of Fludeoxyglucose F 18 Injection have not been established in pediatric patients.

11 DESCRIPTION

11.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[^{18}F]fluoro-D-glucose has the molecular formula of $C_6H_{11}{}^{18}FO_5$ with a molecular weight of 181.26, and has the following chemical structure:



Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.40 GBq (20.0 to 200 mCi) of 2-deoxy-2-[^{18}F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

11.2 Physical Characteristics

Fluorine F 18 has a physical half-life of 109.7 minutes and decays to Oxygen O 16 (stable) by positron decay. The principal photons useful for imaging are the dual 511 keV "annihilation" gamma photons, that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 2).

Table 2. Principal Radiation Emission Data for Fluorine F 18		
Radiation/Emission	% Per Disintegration	Mean Energy
Positron(β+)	96.73	249.8 keV
Gamma(±)*	193.46	511.0 keV

*Produced by positron annihilation
From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-I 1026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 R/hr/mCi (1.35 x 10^{-6} Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb). The range of attenuation coefficients for this radionuclide as a function of lead shield thickness is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding	
Shield thickness (Pb) mm	Coefficient of attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.

Table 4. Physical Decay Chart for Fluorine F 18	
Minutes	**Fraction Remaining**
0*	1.000
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250

*calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fludeoxyglucose F 18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [^{18}F]-FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. Fludeoxyglucose F 18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

12.2 Pharmacodynamics

Fludeoxyglucose F 18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these conditions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging.

In the brain, cells normally rely on aerobic metabolism. In epilepsy, the glucose metabolism varies. Generally, during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

12.3 Pharmacokinetics

Distribution: In four healthy male volunteers, receiving an intravenous administration of 30 seconds in duration, the arterial blood level profile for Fludeoxyglucose F 18 decayed triexponentially. The effective half-life ranges of the three phases were 0.2 to 0.3 minutes, 10 to 13 minutes with a mean and standard deviation (STD) of 11.6 (±) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 4 min.

Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

Metabolism: Fludeoxyglucose F 18 is transported into cells and phosphorylated to [^{18}F]-FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [^{18}F]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[^{18}F]fluoro-6-phospho-D-mannose([^{18}F]FDM-6-phosphate).

Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (ClDG)). Biodistribution and metabolism of ClDG are presumed to be similar to Fludeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (ClDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, ClDG, and ClDM) presumably leave cells by passive diffusion. Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose F 18 that is not involved in glucose metabolism in any tissue is then excreted in the urine.

Elimination: Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Within 33 minutes, a mean of 3.9% of the administrated radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

Special Populations:
The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in renally-impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained [*see Warnings and Precautions (5.2)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the Fludeoxyglucose F 18 Injection carcinogenic potential, mutagenic potential or effects on fertility.

14 CLINICAL STUDIES

14.1 Oncology

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fludeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq.

In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false-positive scans. The efficacy of Fludeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

14.2 Cardiology

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a

blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects).

Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is more limited.

14.3 Neurology

In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185 to 370 MBq (5 to 10 mCi). The mean age was 16.4 years (range: 4 months to 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (14/87) of the patients; in 34% (30/87) of the patients, Fludeoxyglucose F 18 Injection PET images provided new findings. In 32% (27/87), imaging with Fludeoxyglucose F 18 Injection was inconclusive. The impact of these imaging findings on clinical outcomes is not known.

Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL

glass vial containing between 0.740 to 7.40 GBq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-2-[^{18}F]-fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 40028-511-30; 40028-511-50

Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

Store the Fludeoxyglucose F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store and dispose of Fludeoxyglucose F 18 Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.

The expiration date and time are provided on the container label. Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS time.

17 PATIENT COUNSELING INFORMATION

Instruct patients in procedures that increase renal clearance of radioactivity.
Encourage patients to:

- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.

Pregnancy: Advise pregnant women of the risk of fetal exposure to radiation with Fludeoxyglucose F 18 Injection [see Use in Specific Populations (8.1)].

Lactation: Advise lactating women that exposure to Fludeoxyglucose F 18 Injection through breast milk can be minimized by pumping and discarding breast milk and avoiding close (breast) contact with the infant for 9 hours after Fludeoxyglucose F 18 Injection [see Use in Specific Populations (8.2)].

Manufactured and distributed by:

PETNET Solutions, Inc.
810 Innovation Drive
Knoxville, TN 37932

SODIUM FLUORIDE F 18- sodium fluoride f-18 injection, solution
PETNET Solutions, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Sodium Fluoride F 18 Injection safely and effectively. See full prescribing information for Sodium Fluoride F 18 Injection.
SODIUM FLUORIDE F 18 INJECTION
For Intravenous Use
Initial U.S. Approval: January 2011

INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging of bone to define areas of altered osteogenic activity (1).

DOSAGE AND ADMINISTRATION

- Sodium Fluoride F18 Injection emits radiation and must be handled with appropriate safety measures (2.1).
- Administer 300-450 MBq (8–12 mCi) as an intravenous injection in adults (2.4).
- Administer approximately 2.1 MBq/kg in children with a minimum of 19 MBq (0.5 mCi) and a maximum of 148 MBq (4 mCi) as an intravenous injection (2.5).
- Imaging can begin 1–2 hours after administration; optimally at one hour post administration (2.7).
- Encourage patients to void immediately prior to imaging the lumbar spine and bony pelvis (2.7).

DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) of no-carrier-added sodium fluoride F18 at the end of synthesis (EOS) reference time in aqueous 0.9% sodium chloride solution (3). Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Allergic Reactions: As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available (5.1).
- Cancer Risk: Sodium Fluoride F 18 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker (5.2).

ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems (6).

To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Any radiopharmaceutical, including Sodium Fluoride F18 injection, may cause fetal harm. Use only if clearly needed (8.1)
- Nursing: A decision should be made whether to interrupt nursing after Sodium Fluoride F 18 Injection administration or not to administer Sodium Fluoride F 18 Injection taking into consideration the importance of the drug to the mother. (8.3)
- Pediatrics: Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection (8.4).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

- Wear waterproof gloves and effective shielding when handling Sodium Fluoride F 18 Injection. Use

appropriate safety measures, including shielding, consistent with proper patient management to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel, and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Sodium Fluoride F 18 Injection.
- The dose of Sodium Fluoride F 18 Injection should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.
- The final dose for the patient should be calculated using proper decay factors from the time of End of Synthesis (EOS), and measured by a suitable radioactivity calibration system before administration *[see Description (11.2)]*.

2.2 Radiation Safety - Patient Preparation

- To minimize the radiation-absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to ingest at least 500 mL of fluid immediately prior and subsequent to the administration of Sodium Fluoride F 18 Injection.
- Encourage the patient to void one-half hour after administration of Sodium Fluoride F 18 Injection and as frequently thereafter as possible for the next 12 hours.

2.3 Drug Preparation and Administration

- Calculate the necessary volume to administer based on calibration time and dose.
- Inspect Sodium Fluoride F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer Sodium Fluoride F 18 Injection containing particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Aseptically withdraw Sodium Fluoride F 18 Injection from its container.

2.4 Recommended Dose for Adults

Administer 300–450 MBq (8–12 mCi) as an intravenous injection.

2.5 Recommended Dose for Pediatric Patients

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi–4 mCi) were used.

2.6 Radiation Dosimetry

The age/weight- based estimated absorbed radiation doses (mGy/MBq) from intravenous injection of Sodium Fluoride F 18 Injection are shown in Table 1. These estimates were calculated based on human data and using the data published by the Nuclear Regulatory Commission [1] and the International Commission on Radiological Protection for Sodium Fluoride Injection [2]. The bone, bone marrow and urinary bladder are considered target and critical organs.

Table 1: Estimated Absorbed Radiation Doses after Intravenous Administration of Sodium Fluoride F 18 Injection

Organ	Estimated Radiation Dose mGy/MBq				
	Adult 70 kg [1]	15 year 56.8 kg [2]	10 year 33.2 kg [2]	5 year 19.8 kg [2]	1 year 9.7 kg [2]
Adrenals	0.0062	0.012	0.018	0.028	0.052

Brain		0.0056	N/A	N/A	N/A	N/A
Bone surfaces		0.060	0.050	0.079	0.13	0.30
Breasts		0.0028	0.0061	0.0097	0.015	0.030
GI	Gallbladder wall	0.0044	N/A	N/A	N/A	N/A
	Stomach wall	0.0038	0.008	0.013	0.019	0.036
	Small intestine	0.0066	0.012	0.018	0.028	0.052
	Upper large intestine wall	0.0058	0.010	0.016	0.026	0.046
	Lower large intestine wall	0.012	0.016	0.025	0.037	0.063
Heart wall		0.0039	N/A	N/A	N/A	N/A
Kidneys		0.019	0.025	0.036	0.053	0.097
Liver		0.0040	0.0084	0.013	0.021	0.039
Lungs		0.0041	0.0084	0.013	0.020	0.039
Muscle		0.0060	N/A	N/A	N/A	N/A
Ovaries		0.011	0.016	0.023	0.036	0.063
Pancreas		0.0048	0.0096	0.015	0.023	0.044
Red marrow		0.028	0.053	0.088	0.18	0.38
Skin		0.0040	N/A	N/A	N/A	N/A
Spleen		0.0042	0.0088	0.014	0.021	0.041
Testes		0.0078	0.013	0.021	0.033	0.062
Thymus		0.0035	N/A	N/A	N/A	N/A
Thyroid		0.0044	0.0084	0.013	0.020	0.036
Urinary bladder wall		0.25	0.27	0.4	0.61	1.1
Uterus		0.019	0.023	0.037	0.057	0.099
Other tissue		N/A	0.010	0.015	0.024	0.044
Effective Dose Equivalent mSv/MBq		**0.027**	**0.034**	**0.052**	**0.086**	**0.17**

[1] Data from Nuclear Regulatory Commission Report, *Radiation Dose Estimates for Radiopharmaceuticals*, NUREG/CR-6345, page 10, 1996.

[2] Data from ICRP publication 53, *Radiation Dose to Patients from Radiopharmaceuticals* , Ann ICRP, Volume 18, pages 15 and 74, 1987

2.7 Imaging Guidelines

- Imaging of Sodium Fluoride F 18 Injection can begin 1–2 hours after administration; optimally at 1 hour post administration.
- Encourage the patient to void immediately prior to imaging the fluoride F18 radioactivity in the lumbar spine or bony pelvis.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7.400 MBq/mL (10–200 mCi/mL) at EOS reference time of no-carrier-added sodium fluoride F18 in aqueous 0.9% sodium chloride solution. Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.

5.2 Radiation Risks

Sodium Fluoride F 18 Injection may increase the risk of cancer. Carcinogenic and mutagenic studies with Sodium Fluoride F18 injection have not been performed. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

7 DRUG INTERACTIONS

The possibility of interactions of Sodium Fluoride F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Any radiopharmaceutical including Sodium Fluoride F 18 Injection has a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the radionuclide dose. Animal reproductive and developmental toxicity studies have not been conducted with Sodium Fluoride F 18 Injection. Prior to the administration of Sodium Fluoride F 18 Injection to women of childbearing potential, assess for presence of pregnancy. Sodium Fluoride F 18 Injection should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Sodium Fluoride F 18 Injection is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to interrupt nursing after administration of Sodium Fluoride F 18 Injection or not to administer Sodium Fluoride F 18 Injection, taking into account the importance of the drug to the mother. The body of scientific information related to radioactivity decay, drug tissue distribution and drug elimination shows that less than 0.01% of the radioactivity administered remains in the body after 24 hours (10 half-lives). To minimize the risks to a nursing infant, interrupt nursing for at least 24 hours.

8.4 Pediatric Use

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi - 4 mCi) were used. Sodium Fluoride F18 was shown to localize to areas of bone turnover including rapidly growing epiphyses in developing long bones.

Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection.

11 DESCRIPTION

11.1 Chemical Characteristics

Sodium Fluoride F 18 Injection is a positron emitting radiopharmaceutical, containing no-carrier-added, radioactive fluoride F18 that is used for diagnostic purposes in conjunction with PET imaging. It is administered by intravenous injection. The active ingredient, sodium fluoride F18, has the molecular formula Na[^{18}F] with a molecular weight of 40.99, and has the following chemical structure:

Na+ $^{18}F^-$

Sodium Fluoride F 18 Injection is provided as a ready-to-use, isotonic, sterile, pyrogen-free, preservative-free, clear and colorless solution. Each mL of the solution contains between 370 MBq to 7,400 MBq (10 mCi to 200 mCi) sodium fluoride F18, at the EOS reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8. The solution is presented in 30 mL multiple- dose glass vials with variable total volume and total radioactivity in each vial.

11.2 Physical Characteristics

Fluoride F18 decays by positron (β+) emission and has a half-life of 109.7 minutes. Ninety-seven percent of the decay results in emission of a positron with a maximum energy of 633 keV and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 2). Fluorine F18 atom decays to stable ^{18}O-oxygen.

Table 2: Principal Emission Data for Fluoride F18

Radiation/Emission	% per Disintegration	Mean Energy
Positron (β+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

* Produced by positron annihilation

[3] Kocher, D.C. Radioactive Decay Data Tables DOE/TIC-11026, 69, 1981.

The specific gamma ray constant for fluoride F18 is 5.7 R/hr/mCi (1.35 x 10^{-6} Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). A range of values for the attenuation of radiation results from the interposition of various thickness of Pb. The range of attenuation coefficients for this radionuclide is shown in Table 3. For example, the interposition of an 8.3 mm thickness of Pb with a coefficient of attenuation of 0.25 will decrease the external radiation by 75%.

Table 3:Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0	0.00
4	0.50
8	0.25

13	0.10
26	0.01
39	0.001
52	0.0001

Table 4 lists the fraction of radioactivity remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4: Physical Decay Chart for Fluoride F18

Time Since Calibration	Fraction Remaining
0*	1.00
15 minutes	0.909
30 minutes	0.826
60 minutes	0.683
110 minutes	0.500
220 minutes	0.250
440 minutes	0.060
12 hours	0.011
24 hours	0.0001

* Calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluoride F18 ion normally accumulates in the skeleton in an even fashion, with greater deposition in the axial skeleton (e.g. vertebrae and pelvis) than in the appendicular skeleton and greater deposition in the bones around joints than in the shafts of long bones.

12.2 Pharmacodynamics

Increased fluoride F18 ion deposition in bone can occur in areas of increased osteogenic activity during growth, infection, malignancy (primary or metastatic) following trauma, or inflammation of bone.

12.3 Pharmacokinetics

After intravenous administration, fluoride F18 ion is rapidly cleared from the plasma in a biexponential manner. The first phase has a half-life of 0.4 h, and the second phase has a half-life of 2.6 h. Essentially all the fluoride F18 that is delivered to bone by the blood is retained in the bone. One hour after administration of fluoride, F18 only about 10% of the injected dose remains in the blood. Fluoride F18 diffuses through capillaries into bone extracellular fluid space, where it becomes bound by chemisorption at the surface of bone crystals, preferentially at sites of newly mineralizing bone.

Deposition of fluoride F18 in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the fluoride F18. Fluoride F18 does not appear to be bound to serum proteins.

In patients with normal renal function, 20% or more of the fluorine ion is cleared from the body in the urine within the first 2 hours after intravenous administration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess reproductive toxicity, mutagenesis and carcinogenesis potential of Sodium Fluoride F 18 Injection have not been performed.

14 CLINICAL STUDIES

14.1 Metastatic Bone Disease

The doses used in reported studies ranged from 2.7 mCi to 20 mCi (100 MBq to 740 MBq), with an average median dose of 10 mCi (370 MBq) and an average mean dose of 9.2 mCi (340 MBq). In PET imaging of bone metastases with Sodium Fluoride F 18 Injection, focally increased tracer uptake is seen in both osteolytic and osteoblastic bone lesions. Negative PET imaging results with Sodium Fluoride F 18 Injection do not preclude the diagnosis of bone metastases. Also, as benign bone lesions are also detected by Sodium Fluoride F 18 Injection, positive PET imaging results cannot replace biopsy to confirm a diagnosis of cancer.

14.2 Other Bone Disorders

The doses used in reported studies ranged from 2.43 mCi to 15 mCi (90 MBq to 555 MBq), with an average median dose of 8.0 mCi (300 MBq) and an average mean dose of 7.6 mCi (280 MBq).

15 REFERENCES

1. Stabin, M.G., Stubbs, J.B. and Toohey R.E., Radiation Dose Estimates for Radiopharmaceuticals, U.S. Nuclear Regulatory Commission report NUREG/CR-6345, page 10, 1996.
2. Radiation Dose to Patients from Radiopharmaceuticals, ICRP publication 53, Ann ICRP, 18 pages 15 and 74, 1987
3. Kocher, D.C., "Radioactive Decay Data Tables: A Handbook of decay data for application to radiation dosimetry and radiological assessments" DOE/TIC-11026, page 69, 1981.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sodium Fluoride F 18 Injection is supplied in a multiple-dose Type I glass vial with elastomeric stopper and aluminum crimp seal containing between 370 and 7,400 MBq/mL (10–200 mCi/mL) of no carrier-added sodium fluoride F18, at the EOS reference time, in aqueous 0.9% sodium chloride solution. The total volume and total radioactivity per vial are variable. Each vial is enclosed in a shielded container of appropriate thickness.

The product is available in a 30 mL vial configuration with a variable fill volume. The NDC number is:

40028-512-30 (30 mL)

Storage

Store at 25°C (77°F) in a shielded container; excursions permitted to 15–30°C (59–86°F). Use the solution within 12 hours of the EOS reference time.

Handling

Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

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