



White paper

The current role of NaF PET/CT in the evaluation of prostate cancer

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Executive summary

Prostate cancer (PC) is a heterogeneous disease, which will progress to an advanced stage in a subset of patients. Given the high incidence of bone metastases, in high-risk patients (such as those with an elevated PSA level or Gleason score) skeletal imaging plays an important role in the management of PC. PET/CT using the bone-seeking radiopharmaceutical sodium fluoride F 18 injection* (^{18}F NaF) can be an accurate technique for imaging skeletal metastases in these patients. It has also been shown to have a substantial impact on therapy decisions during initial diagnoses of patients with biochemical failure, and in cases of therapy monitoring. The incremental value of this imaging technique for patient management compared to conventional bone imaging is being investigated; especially in patients with very few small skeletal manifestations who might benefit from its high sensitivity. ^{18}F NaF PET/CT imaging is mentioned in several clinical practice guidelines as a valid bone-scanning technique, and in the United States it is reimbursed via Coverage with Evidence Development (CED) and the National Oncologic PET Registry (NOPR).

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 17-24.

Introduction

PC is the second most common cancer in men worldwide. In more developed regions of the world, two-thirds of men are diagnosed with PC¹. It is the most frequent cancer in the United States with an estimated 233,000 new cases in 2014. With 29,480 deaths anticipated in 2014, PC is the leading cause of cancer death in men in the United States. PC occurs mainly in older men and is rare before the age of 40. It is more likely to affect men of African American descent, or those with family history of PC^{2,3}. PC is the most common cancer in European men with an incidence of 416,732 and mortality of 92,237 in 2012⁴.

The aggressiveness of PC varies among different patients. Whereas the majority of PCs will remain localized, there is a subset of patients in whom the cancer will progress and, therefore, require therapeutic intervention⁵. Approximately 4% of all patients present metastasized disease at the initial diagnosis and over time, up to 75% of the patients, with the more aggressive PC type, present bone metastases^{5,6,7,8}. Osteoblastic metastases are the most common site of non-nodal distant disease manifestations in PC patients⁹.

Up to 10 years after radical prostatectomy, as many as 50% of all men experience a detectable rise in prostate-specific antigen (PSA) without other clinical manifestations¹⁰. This is a widespread problem for clinicians.

In addition, around 10-20% of patients develop castration-resistant PC** (CRPC) within approximately five years of follow-up. This advanced form of PC is associated with poor quality of life, low survival rates and metastatic spread. A total of 33% of patients without identifiable metastases at diagnosis of CRPC develop them within two years^{11,12,13}.

The presence or absence of systemic disease is one of the most important factors in influencing the selection of therapy in PC. In each disease stage, the diagnosis of metastases has important therapeutic implications, and the timely and early diagnosis of bone metastases in PC patients is instrumental for patient management^{14,11,7}. The extent of bone metastases is an independent prognostic factor^{22,23}.

**Rising PSA with castrate testosterone level (50 mg/ dL)

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 ethanol as 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 (¹⁸F FDG) see page 3. For full prescribing information see pages 25-36.

¹⁸F NaF PET/CT bone imaging

Positron emission tomography (PET) combined with computed tomography (CT), commonly referred to as PET/CT, plays an increasingly important role in oncology, particularly when using the radiopharmaceutical Fludeoxyglucose F 18 Injection (¹⁸F FDG)^{17,16}. Due to the variable rates of glucose metabolism, not all malignant lesions can be reliably depicted with ¹⁸F FDG¹⁹. ¹⁸F FDG uptake can be low, especially in well-differentiated tumors, which limits the sensitivity of ¹⁸F FDG PET/CT for the staging or follow-up in a substantial subset of patients with PC, in particular those with local, low-grade tumors^{20,21}.

As for bone imaging, in tumors with predominantly sclerotic metastases—such as prostate cancer—¹⁸F FDG is less accurate in assessing skeletal involvement²⁰, as it shows a lower tracer uptake in lesions in comparison to lytic metastases^{41,18,27}.

The bone-seeking radiopharmaceutical ¹⁸F NaF was initially introduced more than 50 years ago. It was originally used for bone imaging with conventional gamma/SPECT cameras, but yielded poor image resolution due to the high energy of the emitting radiation. In the early 1970s, ¹⁸F NaF was replaced by 99m-Technetium (^{99m}Tc) labeled radiopharmaceuticals, which are now the most common radiopharmaceuticals used to evaluate bone metastases. Given the technical advances in PET imaging in the last two decades, ¹⁸F NaF was reintroduced for clinical utilization and research investigations^{30,49}.

Sensitivity and specificity of ¹⁸F NaF bone imaging

The accumulation of ¹⁸F NaF in malignant bone lesions mirrors an increase in regional blood flow and intensified bone turnover in those areas. The high capillary permeability and fast blood clearance of ¹⁸F NaF results in an excellent target-to-background ratio. The combination of the favorable pharmacokinetic characteristics of ¹⁸F NaF with the excellent image resolution of state-of-the-art PET detectors transformed ¹⁸F NaF-based bone imaging into a very sensitive technique for the detection of lytic and sclerotic malignant bone lesions for high-risk patients with PC^{24,18,25}. ¹⁸F NaF accumulates well in benign skeletal lesions with high bone turnover, which impacts the specificity of the technique as a standalone option. The introduction of combined PET/CT systems has significantly improved the specificity of ¹⁸F NaF imaging, because the CT component of the study allows morphologic correlation and characterization of the functional lesion and, therefore, a better differentiation between benign bone lesions and metastases^{24,25,18}. For example, Even-Sapir et al. reported sensitivity and specificity for detection of bone lesions for ¹⁸F NaF-PET/CT (100 and 100%, respectively) compared to ¹⁸F NaF PET alone (100 and 62%, respectively)²⁵.

Bone imaging in high-risk patients with newly diagnosed disease

Clinical perspective

The early detection or exclusion of malignant skeletal involvement is instrumental in managing newly diagnosed patients with high-risk PC. Patients without systematic tumor spreads can gain from a radical localized curative therapy approach. Patients with distant metastases, on the other hand, will potentially benefit from a timely initiated androgen withdrawal and bisphosphonate therapy, and could be spared the harmful side effects from unnecessary radical therapy²⁵.

The Even-Sapir et al. study demonstrated that in 25 high-risk patients* with newly diagnosed PC, the use of the ¹⁸F NaF PET/CT impacted therapy management in 19 patients²⁵ by revealing previously unknown bone metastases or excluding metastatic disease in unspecific sclerotic bone lesions that were diagnosed using a CT-only scan. A Swedish study from 2012 on 90 high-risk patients** who were planned for curative treatment, underwent an ¹⁸F NaF PET/CT scan. The ¹⁸F NaF PET/CT revealed bone metastases in 37 patients (41%), triggering a treatment management change from curative to palliative treatment due to widespread metastatic disease in a subset of those 37 patients²⁹.

The excellent performance of ¹⁸F NaF PET/CT was confirmed by Mosavi et al. They concluded that, based on a study of 49 patients with newly diagnosed PC and a Gleason score of at least 8, ¹⁸F NaF PET/CT is a highly sensitive method to diagnose PC bone metastases, more sensitive than diffusion-weighted magnetic resonance imaging (DW-MRI)²⁶. In another prospective single-center study, a Danish group confirmed the high sensitivity of ¹⁸F NaF PET/CT in revealing bone metastases in 46 hormone-naïve patients with biopsy proven prostate cancer, who had known bone metastases. The median PSA level of the patients was 84 ng/mL and the mean Gleason score of the tumors was 7.7²⁸.

A recent publication presents the very encouraging initial results of the NOPR in the United States, which looked into the impact of ¹⁸F NaF PET/CT on the therapy management of patients with known prostate cancer³⁵. More than 1,000 patients underwent a ¹⁸F NaF PET/CT for initial staging, which triggered, in almost 50% of patients, a change in therapy management. The overall change in intended management was 12% if no effect was assumed for cases in which pre-PET plans included further imaging (imaging-adjusted impact). The authors came to the conclusion that, pending the results of large direct randomized comparisons of ¹⁸F NaF PET/CT and other modalities, "the findings... indicated that ¹⁸F NaF PET had a substantial impact across the common testing indications in prostate cancer"³⁵.

*Either Gleason score of eight or more, and/or PSA levels exceeding 20 ng/mL or nonspecific sclerotic lesions on CT

**Either Gleason score of eight or more, and/ or PSA levels 20-99 ng/mL

Guidelines

National Comprehensive Cancer Network

The clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) recommend a bone scan for patients with a life expectancy of more than five years at the initial diagnosis and any of the following:

- PSA exceeds 10 ng/mL plus Stage T2
- PSA exceeds 20 ng/mL plus Stage T1
- Gleason score of at least 8
- TNM Stage T3 and T4
- Any stage disease with symptoms suggesting bone metastases

According to the NCCN, ^{18}F NaF PET imaging is included in the suggested primary bone scan techniques. In addition, the additional value of a coregistered CT, as it is in a PET/CT scan, is mentioned³¹.

European Society of Medical Oncology

The guidelines of the European Society of Medical Oncology (ESMO) do not recommend bone-specific imaging for patients with low-risk disease.

For those with intermediate-risk, bone scintigraphy (no further specification) should be considered in case of clinical suspicion of bone metastases if the Gleason score is 4+3 or serum PSA exceeds 10 ng/mL. All patients with high-risk disease should undergo a bone scintigraphy³².

European Association of Urology

The guidelines of the European Association of Urology (EAU) recommend bone scans for any patient with symptoms that are suggestive of bone metastases and for any patient with PSA exceeding 10 ng/mL, or a Gleason score of 8 and above or TNM stage 3 or 4. The guideline identifies ^{18}F NaF PET/CT as a new and highly sensitive method of radioisotope-based bone scanning with the potential to impact patient management. The costeffectiveness in using ^{18}F NaF as the primary bone imaging exams still warrants further investigation³³.

Reimbursement

The US Centers for Medicare and Medicaid Services (CMS) reimburses ^{18}F NaF PET/CT scans for the detection of bone metastasis via Coverage with Evidence Development (CED) through the NOPR. This is done in order to collect data regarding the referring physician's treatment plans for Medicare patients with a high likelihood of existing bone metastases. Therefore, data from the referring physician before and after the PET study, as well as from the interpreting physician, are collected. Based on the complete and timely (30 days) delivery of the information, the interpreting physician will be eligible for reimbursement by CMS³⁴.

For Medicare patients without supplemental coverage, there is a 20% deductible.

As for private payers, the coverage of ^{18}F NaF PET/CT varies and will most likely require pre-authorization.

¹⁸F NaF PET/CT and biochemical failure

Clinical perspective

A rising PSA level after successful treatment of localized prostate cancer (known as biochemical failure) may occur years before the actual metastases become clinically evident. Since up to 50% of men experience a biochemical failure after definitive treatment of prostate cancer, the risk stratification of those patients is an important unmet clinical need^{10,8}. A prospective trial on 37 patients with PSA relapses after definitive treatment for prostate cancer allowed the initial conclusion that ¹⁸F NaF PET/CT is useful in the detection of occult metastases. In that particular study, the use of ¹⁸F NaF PET/CT helped detect in 16.2% of the patients occult bone metastases. Of note is that in prostatectomized men, the positive result of the ¹⁸F NaF PET/CT seems to correlate with the increasing PSA level⁸. In a recently published review, Leung et al. concluded that existing data supports the initial conclusion, that ¹⁸F NaF PET/CT is more sensitive and specific than conventional bone imaging for patients with rising PSA after definitive therapy³⁷. The recently published initial results of the NOPR initiative included almost 2,000 patients who had undergone an ¹⁸F NaF PET/CT scan for suspicion of first bone metastases after previously treated local disease³⁵. For 47% of those patients, the elevation or rising of PSA was the sole indication for the scan, whereas 17% were referred for bone pain alone. In 44.1% of those patients, the results of the ¹⁸F NaF PET/CT triggered a change in patient management; the imaging adjusted rate was 15.8%.

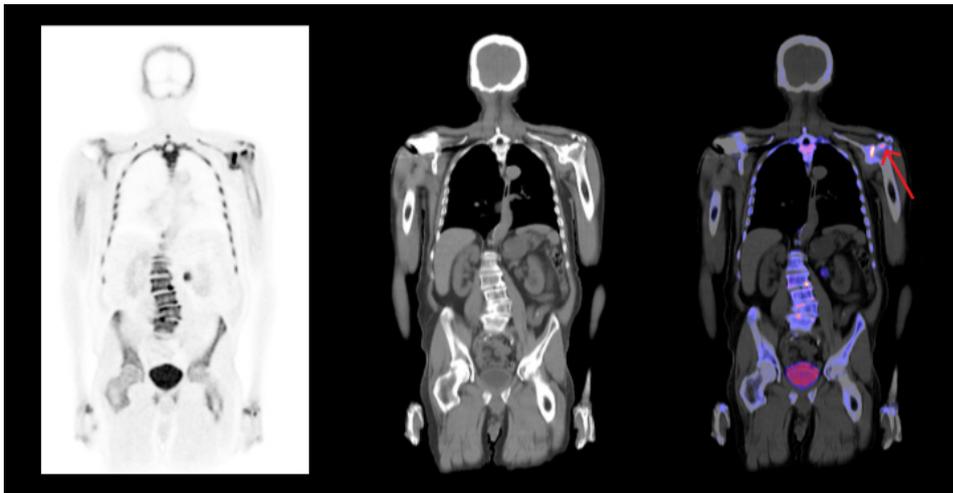


Figure 1: PET Bone Imaging Study with ¹⁸F NaF. Patient Information: 74-year-old male with history of prostate cancer. Gleason score of 7 at time of diagnosis, prostatectomy as initial treatment regimen followed by radiation therapy to pelvic region. PSA continued to rise with value of 2.1. ¹⁸F NaF bone scan was ordered for evaluation of bone metastasis. Image courtesy of Northern California PET Imaging Center, Sacramento, California, USA

Guidelines

National Comprehensive Cancer Network

The NCCN guidelines recommend a bone scan (among other diagnostic tests) for patients with PSA persistence or recurrence after radical prostatectomy or after biochemical failure following external beam radiotherapy*. Either conventional nuclear medicine or ^{18}F NaF PET/CT are recommended³¹. The expert panel elaborates that bone scans are appropriate when patients develop symptoms or when PSA levels are increasing rapidly.

European Society of Medical Oncology

The ESMO guidelines contain no specific recommendation for imaging tests in case of biochemical failure³².

European Association of Urology

For patients who present a biochemical failure after treatment with curative intent, EAU guidelines recommend a bone scan and abdominopelvic CT for patients with a PSA level >10 ng/mL, with high PSA kinetics or in patients with symptoms of bone involvement. The guidelines also discuss ^{18}F NaF PET/CT's high sensitivity in comparison to conventional bone imaging and the authors discuss potential limitations, such as false positive results³³.

Reimbursement

As indicated above, Medicare beneficiaries who are referred for ^{18}F NaF PET/CT imaging for the evaluation of bony metastatic disease are eligible to participate in the CED such as NOPR³⁴.

^{18}F NaF PET/CT and follow-up of bone metastases

Clinical perspective

For patients with CRPC, several new treatment options, such as, taxanes and immunotherapies, have been approved by the US FDA recently based on positive results from clinical trials. These new drugs might require more imaging to monitor treatment response³⁹. Bone scans are the most common method for monitoring bone metastases in patients with advanced PC in connection with treatment.

Qualitative assessment

Under the NOPR initiative, around 500 men underwent an ^{18}F NaF PET/CT scan for suspicion of progressing known bone metastases. This resulted in a more than 50% patient management change; the imaging adjusted rate was 12.4%³⁵.

Quantitative assessment

With the attempt to quantify treatment response based on conventional bone scans, different methods of standardization have been proposed, including a mechanism called Bone Scan Index (BSI)^{39,40}. The BSI derived from conventional bone scans is a prognostic metric of survival and its value as an indicator of response or progression is under investigation. Further research will show if the three-dimensional, quantitative and anatomical information as it is potentially provided by an ^{18}F NaF PET/CT scan, will optimize these metrics even further. Also, whether ^{18}F NaF PET/CT will provide more meaningful, most likely quantitative, information regarding treatment response and

*PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after external beam radiotherapy

disease progression than conventional bone scintigraphy does³⁸. An encouraging publication from 2011 looked into ¹⁸F NaF PET/CT-based quantitative response assessments in five patients with CRPC and bone metastases with no known soft tissue disease, who received Radium-223-chloride (Alpharadin) therapy. The semi-quantitative ¹⁸F NaF PET/CT was more accurate than the qualitative comparison of scans in helping assess responses in bone metastases and correlating with the PSA response and alkaline phosphatase activity. For those patients, the 12-week assessment of ¹⁸F NaF uptake was a closer predictor of the biochemical PSA response than at 6 weeks. The authors concluded that there might be a future role of quantitative ¹⁸F NaF assessment as a potential imaging biomarker for monitoring treatment response in bone metastases after treatment with Ra-223-Chloride. They also encourage further research into using ¹⁸F NaF PET/CT as a biomarker of response in bone metastases in a variety of cancers and treatment types⁴¹.

Guidelines

National Comprehensive Cancer Network

For patients with systemic second-line therapy for CRPC, NCCN recommends close monitoring with radiological imaging (i.e., CT, bone scan) and other tests. Of note is that bone scans are considered inadequate to assess response to treatment with Sipuleucel-T for patients with CRPC³¹.

European Society of Medical Oncology

The ESMO guidelines contain no specific direct recommendation for nuclear medicine imaging tests to assess and monitor existing bone metastases³².

European Association of Urology

The EAU guidelines do not include specific guidance on the use of bone scans for monitoring patients with bone metastases³³.

Reimbursement

Those Medicare beneficiaries who are referred for ¹⁸F NaF-PET/CT for evaluation of bony metastatic disease are eligible to participate in the CED such as NOPR³⁴.

¹⁸F NaF PET/CT and conventional bone scintigraphy

In recent years, a few studies compared the accuracy of ¹⁸F NaF PET/CT with conventional bone scintigraphy for detection of skeletal metastatic disease. The published data shows, for example, that ¹⁸F NaF PET/CT imaging has a higher sensitivity and specificity than a conventional bone scan does^{25,43,20,36,45}. A meta-analysis by Tateishi confirmed the excellent diagnostic performance for revealing bone metastases; the pooled sensitivity and specificity were 96.2% and 98.5%, respectively, on a patient basis and 96.9% and 98.0%, respectively, on a lesion basis⁴⁸. The impact of ¹⁸F NaF PET/CT on PC patient management if a conventional bone scan is performed first is so far unknown⁴³. As for the NOPR³⁵ patients, only a few patients (less than 10%) had prior conventional bone scans, and the additional value of ¹⁸F NaF PET/CT compared to conventional imaging will need to be evaluated. The higher diagnostic accuracy of ¹⁸F NaF PET/CT may help to include more patients with lower PSA levels than those requested by the guidelines⁷ and ¹⁸F NaF PET/CT imaging as a first imaging study might have additional value in identifying patients with early skeletal metastatic disease who have a few small metastatic lesions⁴³. The results of a large randomized comparison⁴⁶ will, hopefully, help to identify those patients who might benefit the most.

Conclusion and outlook

PET/CT imaging using ^{18}F NaF is a very sensitive tool to assist the physician detect malignant skeletal involvement in patients with PC. According to NOPR, ^{18}F NaF PET/CT imaging has high overall impact, especially in relation to its effect on replacing the intended use of other advanced imaging technologies. What is more important is that in 44%-52% of patients, the intended management changed from treatment to non-treatment or vice versa³⁵. Even though ^{18}F NaF PET/CT imaging is more accurate than conventional nuclear medicine bone scans, the incremental benefit with respect to patient management is being investigated. Also, the additional quantitative information derived from this PET/CT image might provide additional valuable information for response management, prognostication and therapy planning for radionuclide therapy. The anatomical information provided by the co-registered CT increases the specificity of ^{18}F NaF PET/CT imaging. Future data will show if a combined PET/MR device will allow an even better lesion characterization, especially in cases with bone marrow infiltration⁵⁰.

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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

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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

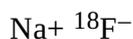
In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi - 4 mCi) were used. Sodium Fluoride F18 was shown to localize to areas of bone turnover including rapidly growing epiphyses in developing long bones.

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:



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 (\pm)*	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 (1.35×10^{-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.

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

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16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

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* 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 human² data and using the data published by the International Commission on Radiological Protection⁴ for Fludeoxyglucose ¹⁸F. 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.

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 Fludeoxyglucose 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

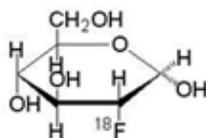
The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight 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-2-¹⁸F-fluoro-D-glucose has the molecular formula of C₆H₁₁¹⁸FO₅ 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-[¹⁸F]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(\pm)*	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 (1.35×10^{-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 [¹⁸F]-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 (\pm) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (\pm) 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 (CIDG)). Biodistribution and metabolism of CIDG 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 (CIDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (CIDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, CIDG, and CIDM) 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 administered 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-[¹⁸F]-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 \(8.2\)](#)].

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