



White paper

The current role of FDG PET/CT in the evaluation of breast cancer

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Executive summary

Positron Emission Tomography combined with Computer Tomography (PET/CT*) using Fludeoxyglucose F 18 Injection (FDG)** can impact staging and restaging of breast cancer, especially in patients with inflammatory, locally advanced and metastatic breast cancer. In addition FDG PET/CT can be very helpful in assessing recurrent cancer, especially in scenarios where previous local treatments changed the morphology and made restaging very challenging.

FDG PET/CT is represented in breast cancer treatment guidelines and reimbursed in certain countries. Encouraging data showing the potential of PET/CT in early therapy monitoring will hopefully lead to the development of PET/CT-based response criteria for the different groups of breast cancer patients. The newest technical developments in scanner technology might additionally contribute to strengthening and expanding the role of clinical PET/CT in breast cancer care.

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

* In this document, the term PET/CT includes PET and PET/CT.

**For indications and important safety information for Fludeoxyglucose F 18 injection (¹⁸F FDG) see page 3. For full prescribing information see pages 20-31.

Introduction

Breast cancer is the most frequently diagnosed cancer among women in 140 of 184 countries worldwide and the most common cause of cancer death among women¹. In 2012, 1.7 million women were diagnosed with breast cancer and 522,000 died from the disease¹. Since the 2008 estimates, the breast cancer incidence has increased by more than 20%, while mortality has increased by 14%¹. The incidence rates vary significantly worldwide, with the lowest number of new cases in Africa and the highest (up to circa 90 of 100,000 women) in the developed nations². In the US, circa 250,000 new cases were expected in 2013, and circa 40,000 patients were estimated to die from breast cancer in 2013³.

Imaging is an instrumental part of managing breast cancer patients and provides important information to surgical, pathologic, and clinical staging^{4,5}.

Positron Emission Tomography (PET) combined with CT (PET/CT) plays an increasingly important role in many oncologic indications^{6,7}. By visualizing the pattern of distribution of FDG *in-vivo*, it can accurately stage many tumors⁸, provide important diagnostic information for detecting selected primary tumors⁹ and support radiation treatment planning¹⁰, therapy monitoring^{11,12} and follow up¹³.

Initial publications more than 10 years ago demonstrated the potential of FDG imaging in the particular indication of breast cancer & breast cancer management^{14,15}. Since then, technical advances and the results of clinical trials support the increasing role of PET/CT in breast cancer staging and restaging and its potential to provide clinically relevant information for treatment monitoring and prognostication.

The heterogeneity of FDG uptake in breast cancer

In addition to the tumor stage according to TNM, factors such as prognosis, therapeutic strategy and prediction of a patient's outcome to therapy depend on additional parameters—for example histology type of the breast cancer, steroid receptor status or expression of the HER2/neu* receptor¹⁶.

The uptake of FDG varies in different types of breast cancer^{17,18}. The FDG avidity of an infiltrating ductal carcinoma, for example, exceeds that of an infiltrating lobular carcinoma. On the other hand, the FDG uptake in a ductal carcinoma *in situ* is usually weak^{18,19,17}. The FDG accumulation also correlates with the histological tumor grade and the immunohistochemical expression of the proliferation marker Ki67^{18,19}. Research looking into the associations between steroid hormone receptor status, HER2 expression and p53 status and FDG uptake led to contradictory results^{19,20,21,18,22}. More recent studies on larger patient numbers showed a higher FDG uptake in estrogen receptor–negative tumors than in those with estrogen receptor expression^{18,23}. Triple-negative breast tumors** are an aggressive subtype of breast cancer with poor prognosis and limited therapeutic options and have demonstrated a relatively high FDG avidity^{5,6,9}.

The currently existing data point to the conclusion that FDG uptake in the primary breast tumor correlates with several factors, which are related to a poorer prognosis^{18,22}.

Primary diagnosis of breast lesions

Current status

When using a specific “mammography” protocol using supine and delayed prone PET acquisition as well as contrast enhanced CT, PET/CT achieved an equivalent diagnostic accuracy to MR for the detecting breast cancer lesions^{24,25}. The high detection rate of breast cancer lesions in the Heusner study—75% of all small T1b tumors were detected by PET/CT—is in contrast with a publication where PET/CT showed a modest sensitivity for smaller tumors. The modest sensitivity is mainly attributed to the low FDG accumulation in low-grade or lobular carcinoma and/or the limited spatial resolution of the PET/CT scanner¹⁸.

Dual-time-point PET/CT imaging has the potential to improve both the sensitivity and specificity of FDG breast imaging. Adding a delayed image to the whole-body scan can significantly increase the FDG accumulation in the image and lead to better sensitivity^{26,27}. Dual-time-point imaging proved to be especially useful in patients with carcinoma *in situ*, invasive small lesions, invasive lobular and mixed types of carcinomas^{26,27}. Assessing the pattern of the FDG accumulation over time also helps to increase the specificity and to better differentiate primary breast cancer from benign breast tumors or inflammatory processes^{18,28}.

Of importance is that incidental findings of increased FDG accumulation in the breast need to be further explored as they can represent breast cancer in a significant percentage of the patients²⁹.

* The Her2/neu receptor is an important prognostic biomarker and target of therapy for a subgroup of breast cancer patients.

** Tumors with neither steroid nor HER2 receptor expression.

Currently, PET/CT has no significant clinical role in the diagnostic workup of suspicious breast lesions. Nevertheless, positron emission mammography (PEM) using an organ-specific PET device with high spatial resolution showed promising results in detecting smaller breast tumors with comparable sensitivity to MR^{30,31}. Clinical data suggest that PEM can provide very useful information in detecting breast malignancies and for guiding biopsies.

Guidelines

Neither the current versions of national guidelines nor the European Society of Medical Oncology (ESMO) clinical guidelines mention PET/CT in the context of primary diagnosis of breast cancer.

Reimbursement

The evaluation of suspicious breast lesions by FDG PET is not covered by the Centers for Medicare & Medicaid Services (CMS). Nevertheless, the use of PET for the Initial Anti-tumor Treatment strategy evaluation of a patient with axillary lymph node metastasis of a cancer of unknown primary origin or of a patient with a paraneoplastic syndrome that might possibly be caused by an occult breast cancer are covered³².

Pretherapeutic staging

Accurate and reliable initial staging in breast cancer is instrumental for therapy selection and prognostication. Many encouraging results underline the potential of FDG PET/CT for breast cancer staging. As with most imaging tests, the diagnostic accuracy and clinical value of FDG imaging often depends on the individual clinical question. PET/CT may be able to decrease the total number of imaging studies used for staging to rule out distant metastatic disease³³, whereas its limited sensitivity to detect axillary lymph node involvement will still require sentinel lymph node biopsy for axillary staging.

Current status

T staging and detection of multifocality

PET/CT “mammography” using a supine/prone protocol on a regular PET/CT scanner may be more accurate than MR in differentiating breast lesions as unifocal, multifocal, or multi-centric²⁴.

Axillary staging in early-stage tumors

FDG uptake in an axillary node has a high positive predictive value of more than 80% in a non-infectious setting^{34,35}. FDG accumulation in this area is therefore suggestive of malignant disease and direct axillary lymph node dissection or ultrasound guided fine needle biopsy of the lesion is recommended¹⁸.

More than 20 years ago, initial data on more than 160 patients suggested that FDG imaging might be an accurate noninvasive technique to predict axillary node involvement¹⁵—the reported sensitivity was 94.4% with a specificity of 86.3%. Since then, the capability of PET and PET/CT to assess axillary lymph node involvement in early stage tumors has been studied intensely^{4,36}. It became apparent that, especially

for smaller breast tumors, PET/CT was not able to reliably identify axillary lymph node involvement, is not routinely recommended for axillary staging of patients with newly diagnosed breast cancer and cannot replace sentinel node biopsy.

Staging in stage II-III disease and inflammatory breast cancer

As for patients with more advanced stage breast cancer, PET/CT often provides critical information and is considered to be superior to conventional staging for the detection of unforeseen, internal mammary chain nodes or distant metastatic disease. For example^{37,38,18,39,40}, in almost one-third of patients with stage II-III breast cancer, PET/CT was able to detect additional extraaxillary lymph node involvement, which potentially impacted surgery and radiation therapy^{38,41}.

Inflammatory Breast Cancer is an aggressive form of breast cancer, which has the poorest prognosis among primary breast tumors. 30% of all patients present distant metastases when diagnosed^{4,42} (Figure 1) PET/CT appeared to provide invaluable contributions in assessing the nodal status and distant metastases in patients with inflammatory breast cancer⁴³, and should be considered as initial staging modality for those patients⁴².

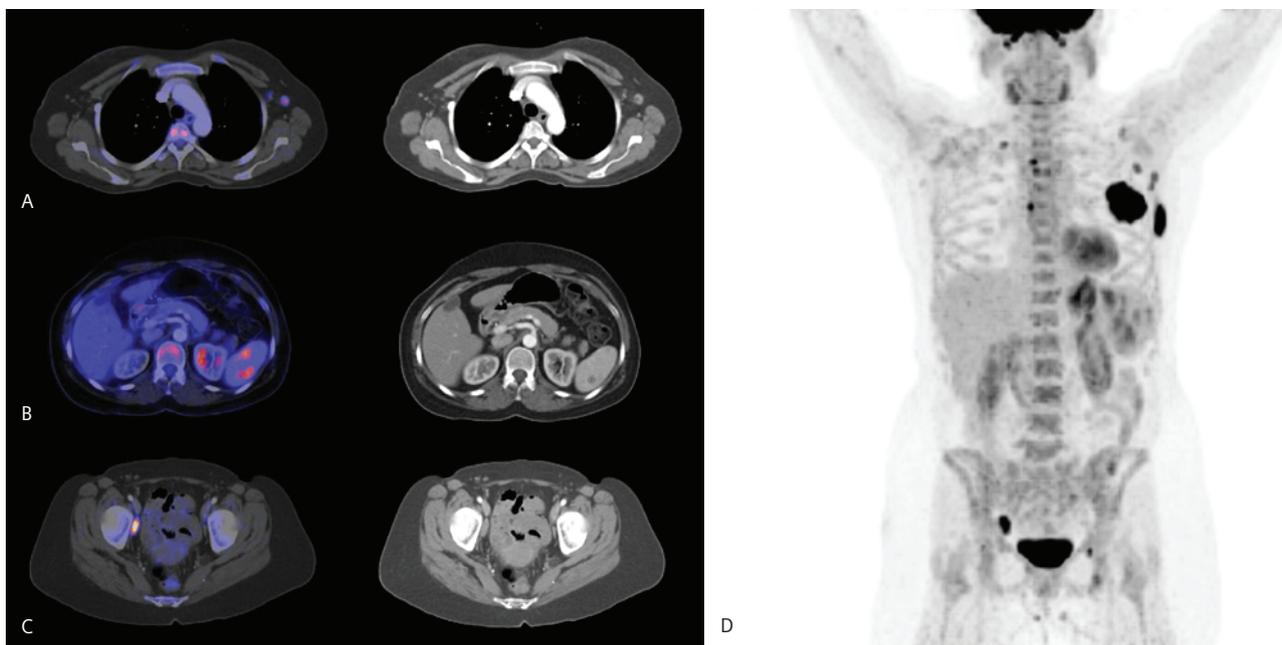


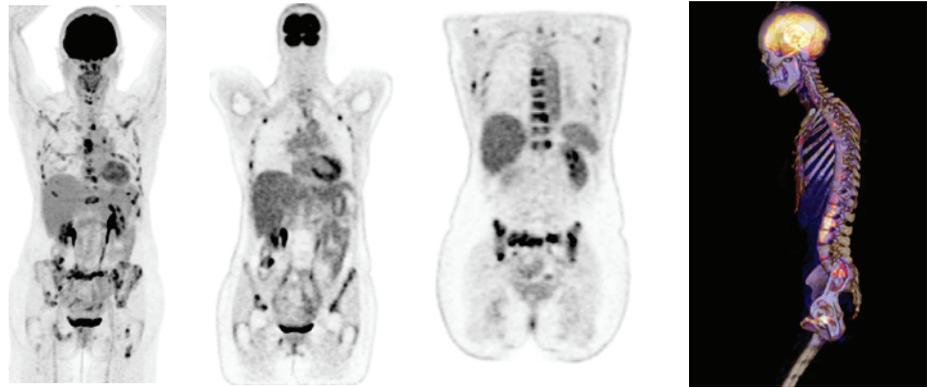
Figure 1: PET/CT of a 51-year old Caucasian female, with an inflammatory breast cancer on the left breast. The tumor was estrogen and progesterone receptor positive, HER2neu status negative. A bilateral breast MRI confirmed a malignant breast lesion with associated skin thickening and tissue retraction and was highly suspicious for left axillary lymphadenopathy and sternal lesion. The FDG/PET CT revealed a hypermetabolic left breast mass consistent with primary breast cancer as well as three left axillary FDG-avid lymph nodes, in agreement with metastatic lymph node spread. (A) FDG accumulation in splenic hypodense lesions (B) as well hypermetabolic right pelvic sidewall lymphadenopathy, (C) all consistent with metastatic disease. (D) The PET/CT showed additional multiple hypermetabolic lytic lesions throughout axial skeleton. An additional Nuclear Medicine bone scan depicted metastases to skull, manubrium, ribs, spine, left scapula, and right distal femur. The patient was diagnosed with Stage IV breast cancer; the suggested treatment was Neoadjuvant chemotherapy with Taxotere, Adriamycin and Cyclophosphamide, followed by a modified radical mastectomy. Data courtesy of University of Tennessee Medical Center

FDG-PET/CT and distant breast cancer metastases

Skeleton

The most common site of distant breast cancer metastases is the skeleton; both, osteolytic and osteoplastic metastases can occur⁴. Many studies suggest that FDG imaging outperforms CT and bone scintigraphy for diagnosing bone marrow lesions as well as lytic or mixed bone metastases^{44,45,46,47,48}. The anatomical information provided by the CT often helps to improve sensitivity for the detection of purely sclerotic bone lesions^{39,18}. The relatively high diagnostic accuracy of FDG PET/CT for detecting bone metastases in breast cancer patients⁴⁹ motivated several researchers to use it as the gold standard^{50,51} (Figure 2). The quantification of the skeletal uptake of FDG PET/CT may provide additional relevant prognostic information; for example a study from 2012 suggested that an increased FDG uptake in bone lesions was correlated with inferior survival in patients with newly diagnosed and untreated bone lesions⁵².

Figure 2: FDG PET/CT for staging of a 51 year-old female patient (59 kg/130 lbs.) with breast cancer. The images show multiple metastases, especially multiple bone metastases. Data courtesy of Centre Hospitalier Princesse Grace, Monaco, Prof. P. Rigo



The bone-seeking PET/CT imaging tracer Sodium Fluoride F 18 Injection (NaF)* has great potential in breast cancer bone imaging. It has been shown to be highly accurate for detection and characterization of lytic and as well as of sclerotic lesions^{53,54}. Figure 2: FDG PET/CT for staging of a 51 year-old female patient (59kg/130 lbs.) with breast cancer. The images show multiple metastases, especially multiple bone metastases. Data courtesy of Centre Hospitalier Princesse Grace, Monaco, Prof. P. Rigo

Extra-Skeletal Metastases

The timely detection of pulmonary metastasis is important for accurate staging and assessing the likelihood of surgical clearance. Patients with higher risk of pulmonary metastases are often evaluated with CT or FDG PET/CT. Compared to standalone CT the metabolic information provided by the PET/CT can increase the specificity of the exam and can facilitate the classification of suspicious indeterminate lesions⁵⁵, especially if they are at least eight millimeters in diameter. Also, the reviewing physicians need to be aware of the potential risk of false positive PET/CT findings—mainly due to radiation pneumonitis, pneumonia, and granulomatous disease.

The high metabolic activity of the liver tissue limits the diagnostic accuracy of the PET/CT in detecting liver metastases. Adrenal metastatic lesions often show a very high FDG avidity; however due to a significant number of benign reasons for high FDG uptake, further characterization is recommended. As for the diagnosis of brain metastases the usefulness of FDG is limited by the physiological, background, metabolic activity in the brain and the limited spatial resolution of the PET detector⁴.

Guidelines

National guidelines

Invasive Breast Cancer

The current version of national oncology guidelines points out that PET/CT is most beneficial when conventional staging leads to unclear or suspicious findings; PET/CT also has a role in depicting unsuspected regional nodal and distant metastatic disease especially for patients with locally advanced or metastatic disease. All recommendations for PET/CT are category 2B⁴. PET/CT for staging of clinical stage I – IIB patients is not recommended.

If a lumpectomy or mastectomy with surgical axillary staging reveals at least four lymph node metastases, PET/CT can be useful to systemically stage patients with clinical Stage I, IIA and B and the operable Stage IIIA (T3, N1, M0). For all patients with T3, N1, M0 (IIIA) and advanced, inoperable stage III disease, FDG PET/CT can be considered and has a potential role in detecting regional node involvement, as well as distant metastases in those patients. As for metastatic disease and stage IV cancer, FDG PET/CT may be beneficial especially in situations with equivocal or suspicious findings in conventional imaging.

If FDG PET/CT is performed and clearly indicates bone metastases, on both the PET and CT component, additional bone-scan or sodium fluoride PET/CT may not be needed⁵.

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

⁴Category 2B: Based upon lower-level evidence, there is industry consensus that the intervention is appropriate. For full prescribing information see pages 32-39.

Inflammatory breast cancer

According to the guidelines, the main contribution of FDG PET/CT in staging of inflammatory breast cancer is for patients with unclear or suspicious findings in the conventional staging. Due to the increased risk of regional lymph node involvement and distant metastases in this group of patients, the expert panel recognizes that FDG PET/CT may have a role as a complementary, standard staging technique. Guidelines recommend the use of either sodium fluoride PET/CT or a nuclear medicine bone scan to screen for bone metastases in asymptomatic patients. Those tests would be obsolete if an FDG PET/CT scan clearly indicated skeletal metastases⁵.

European Society of Medical Oncology (ESMO)

Primary breast cancer

The ESMO practice guideline for primary breast cancer does not support the use of FDG PET/CT in the staging of loco-regional disease but acknowledges that in situations with inconclusive conventional imaging results, FDG PET/CT can be potentially useful⁵⁶.

Locally recurrent or metastatic Breast Cancer According to the ESMO guideline for locally recurrent or metastatic breast cancer, FDG PET/CT can be helpful in the diagnostic workup in specific situations, for example to characterize and classify lesions, which are inaccessible to biopsy and may have a role in detecting very early metastatic disease⁵⁷.

Reimbursement

CMS covers FDG PET scans for M-staging (presence of distant metastasis) in high-risk patients with breast cancer, as well as the use of PET for guiding the Initial Anti-tumor Treatment Strategy evaluation of patients with axillary lymph node metastasis of a cancer of unknown primary origin or of patients with a paraneoplastic syndrome, which might possibly be caused by an occult breast cancer³².

Therapy monitoring

Current status

Early response assessment

Neoadjuvant chemotherapy (NAC) was initially used only for locally advanced or inflammatory breast cancer but is now often applied to preoperatively shrink the tumor size in large, operable tumors^{58,18,28}. Early and reliable prediction of treatment response of the primary breast cancer may allow changing the treatment strategy in case of an ineffective therapy and can save the patient unnecessary side effects. Several publications suggested a correlation between early changes in the FDG uptake, measured by the Standard Uptake Value (SUV) after one or two courses of chemotherapy and the ultimate histopathologic response at completion of chemotherapy^{28,59,58,60,61,62,63,64,65}. A review publication in 2009 concluded that FDG PET/CT potentially allows a response prediction after the first cycle of chemotherapy²⁸. To differentiate responders from non-responders, an optimal threshold value for the changes in SUV needs to be determined¹⁸. Any standardized cutoff value must be carefully chosen and validated in prospective clinical trials for the different types of breast cancer before the results of the PET/CT scan actually trigger the discontinuation of a chemotherapy^{18,28,66}.

⁴Category 2B: Based upon lower-level evidence, there is industry consensus that the intervention is appropriate. For full prescribing information see pages 32-39.

FDG PET/CT is a very promising technique for early assessment of treatment response in patients with metastatic breast cancer^{18,67,68}. The additional information provided by the CT component of the PET/CT scan can, for example, help to better estimate response duration⁶⁹ or to detect mixed responses⁷⁰.

Post therapy evaluation

The availability of data regarding PET/CT-based response assessment after completion of treatment is limited;⁷¹ the combination between PET and CT seems to be especially helpful in evaluating bone metastases⁶⁹. To avoid false negative results caused by metabolic stunning, it is advised to wait at least four to six weeks after completion of the therapy⁷¹. Further prospective multi-center trial studies are needed to better understand the role and reliability of a metabolic response and its prognostic, and potentially, therapeutic consequences⁷¹.

Assessment of endocrine and other targeted therapy

Endocrine therapy has become an important part of systemic breast cancer therapy in women with estrogen-receptor, positive breast cancer⁷². A pilot study in 2012 on 22 women showed that the differences in FDG PET/CT at baseline and after a mean of 10 ± 4 weeks were predictive for the patient's progression-free survival⁷³.

Of importance is the potential occurrence of a metabolic flare phenomenon, which manifests with sudden, treatment-induced worsening of tumor related symptoms and potential signs of disease progression in imaging, such as FDG avid lymphadenopathy. Interestingly, the metabolic flare phenomenon occurring within the first one to two weeks of endocrine therapy is caused by the initial agonist effect of tamoxifen and seems to be predictive for a positive response to endocrine therapy^{74,75,76,55}.

As for therapy with HER2/neu-targeting antibodies or tyrosine kinase inhibitors, a recent, encouraging publication showed that early metabolic assessment by FDG PET/CT was able to identify those patients with a likely response to therapy⁷⁷.

Guidelines

Industry guidelines conclude that due to the lack of reproducible validated and widely accepted standardization for disease activity assessment, PET/CT imaging for monitoring metastatic disease is challenging. The panel classifies FDG imaging as optional for baseline studies and for restaging in case of progressive disease and concluded that there is currently not enough data to provide tangible guidance when monitoring the response to chemotherapy or endocrine therapy⁵.

ESMO

The ESMO guideline for locally recurrent or metastatic breast cancer points out that the contribution of PET/CT to response assessment is still being investigated but that it may be used to determine disease progression⁵⁷.

Reimbursement

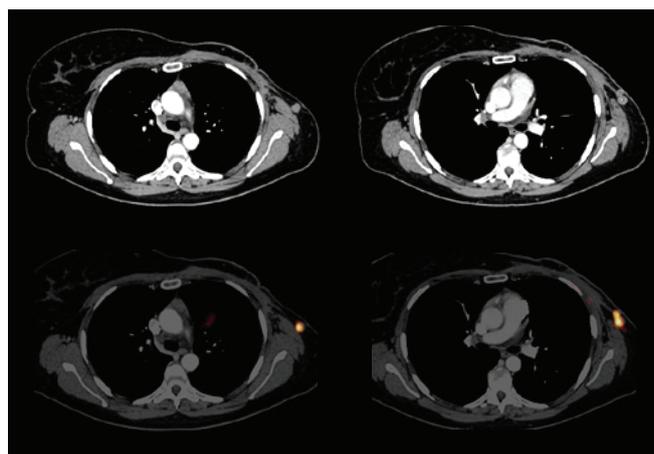
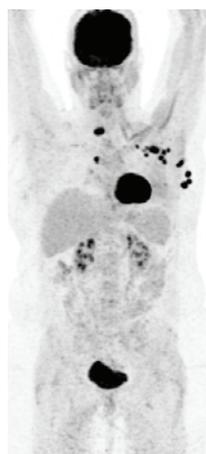
CMS approved reimbursement for FDG in monitoring response to therapy (=Subsequent Anti-tumor Treatment Strategy) in patients with breast cancer³².

Restaging

For patients with a clinical, biochemical or structural suspicion of a relapse, PET/CT seemed to outperform conventional imaging as well as standalone PET^{78,79} and triggered changes in therapy management in a substantial number of patients^{80,108} (Figure 3). In one study, for example, PET/CT detected tumor deposits in 40 out of 89 patients with rising tumor markers, who did not present any clinical symptoms and had no abnormalities in conventional imaging⁸⁰. Those results led the authors to suggest introducing regular follow-up screening based on tumor markers and FDG PET/CT.

Based on a published review of seven publications,¹⁸ the following performance parameters for FDG PET/CT in restaging of breast malignancies can be derived: sensitivity 85%–97%, specificity 52%–100%, and accuracy 60%–98%.

Figure 3: 43-year-old patient (97 kg / 214 lbs.) with a history of breast cancer, FDG PET/CT for restaging. The exam shows multiple metastases; located in the left axilla, adjacent to the left thoracic wall and para-tracheal on the right side. The axillar lymph nodes measure one to two centimeters in diameter. Data courtesy of University Hospital of Antwerpen, Edegem, Belgium



Guidelines

In the workup of recurrent cancer, FDG PET/CT may be beneficial especially in situations with equivocal or suspicious findings in conventional imaging (category 2B). As mentioned above, if FDG PET/CT clearly indicates bone metastases, on both the PET and CT component, bone-scan or sodium fluoride PET/CT may not be needed⁵.

As for follow up and surveillance, guidelines conclude that PET/CT scans in the asymptomatic patient currently provide neither an advantage in survival nor the ability to improve management of patients with recurrent disease.

ESMO

The ESMO guideline for locally recurrent or metastatic breast cancer suggests that FDG PET/CT can be helpful in the diagnostic workup in specific situations, in particular when the location of the recurrent tumor could not be detected or when standard imaging results were inconclusive or conflicting. In addition, FDG PET/CT can be helpful to confirm an isolated recurrence—a situation where patients might benefit from a more aggressive treatment. Lastly, FDG PET/CT can be used to characterize and classify lesions, which are inaccessible to biopsy and may help in detecting very early metastatic disease⁵⁷.

Reimbursement US

CMS covers FDG PET in restaging as a part of the Subsequent Anti-tumor Treatment Strategy in patients with breast cancer. As of mid 2013, three FDG PET scans are covered when used to guide subsequent therapy management after completion of initial anti-tumor therapy. The approval of any additional FDG PET scans beyond those three scans will be determined by local Medicare Administrative Contractors³².

The impact of technological advances—outlook

Currently, FDG PET/CT can provide instrumental information to many aspects of breast cancer staging, treatment, and follow-up.

The potential introduction of dedicated Positron Emission Mammography (PEM) scanners to clinical routine is the subject of several investigations, especially for diagnosis of breast cancer,³⁰ as well as biopsy guidance. A recently published review predicted a possible role of PEM as a first-line tool in cancer screening and diagnosis³¹.

Given the complementary role of MR and PET in breast imaging⁸², combined PET/MRI systems might have a positive impact on breast cancer imaging. Of course, research and clinical trials will have to provide the needed evidence and identify those patients who will have the main benefit. One may anticipate that the combination of the high-resolution, soft-tissue information provided by MR with the highly-specific metabolic information provided by PET will strengthen the position of nuclear, hybrid imaging, especially for diagnosis, T-staging, patients with brain or liver metastases and the management of patients with suspected recurrence.

As for reimbursement, CMS clarified in 2013 that integrated FDG PET/computerized tomography (FDG PET/CT) and integrated FDG PET/magnetic resonance imaging (FDG PET/MRI) are included in the term FDG PET. According to CMS, this decision however did not imply any reconsideration determining any change in coverage either for CT or for MRI imaging³².

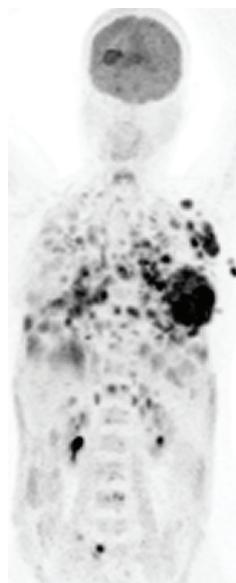
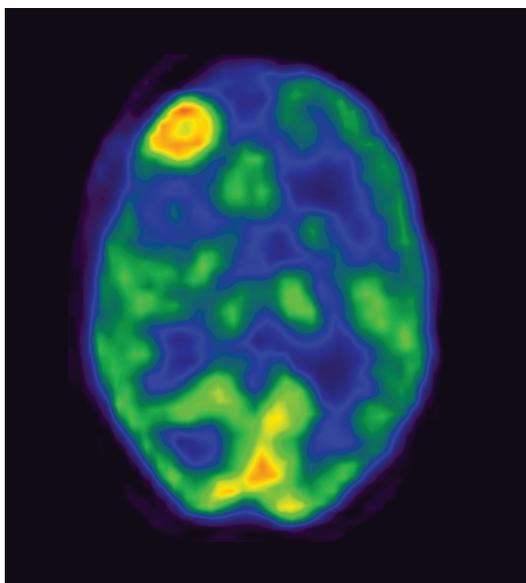


Figure 4: A patient with breast cancer was scanned with a newest generation PET/CT device for staging. In addition to disseminated tumor manifestations in the trunk, the PET/CT also revealed an FDG accumulation right frontal, suggesting an unknown brain metastases, which was confirmed by MR. This new finding could potentially support the decision for an intrathecal chemotherapy application. Image courtesy of Kantonsspital Baselland, Liestal, Switzerland

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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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- 1.2 Cardiology
- 1.3 Neurology

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- 2.2 Recommended Dose for Pediatric Patients
- 2.3 Patient Preparation
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- 2.5 Radiation Safety – 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

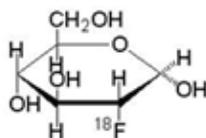
The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight 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.

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 \(8.2\)](#)].

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*

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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
	Stomach wall	0.0038	0.008	0.013	0.019
	Small intestine	0.0066	0.012	0.018	0.028
	Upper large intestine wall	0.0058	0.010	0.016	0.026
	Lower large intestine wall	0.012	0.016	0.025	0.037
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

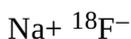
In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi - 4 mCi) were used. Sodium Fluoride F18 was shown to localize to areas of bone turnover including rapidly growing epiphyses in developing long bones.

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.

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