Fludeoxyglucose F 18 Injection, USP **For intravenous use**

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.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- **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 administration.

ADVERSE REACTIONS

Hypersensitivity reactions with pruritus, edema and rash have occurred; have emergency resuscitation equipment and personnel immediately available.

- **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.**

Rx Only

See package insert for full prescribing information.

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PETNET Solutions Inc.
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Knoxville, TN 37932

Distributed by:
PETNET Solutions Inc.
810 Innovation Drive
Knoxville, TN 37932

PETNET Solutions

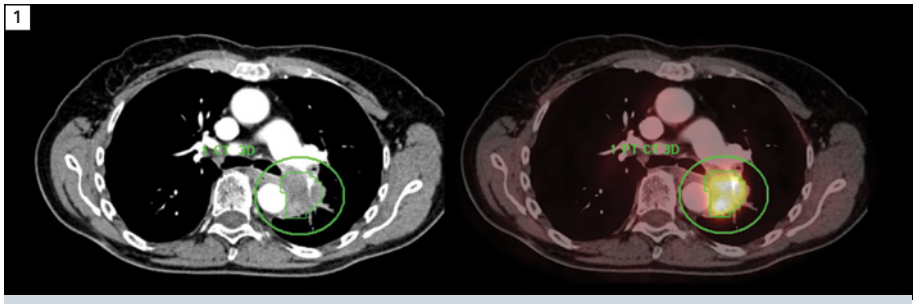
^{18}F FDG PET•CT and Lung Cancer: Increasing Accuracy in Radiation Therapy Planning

^{18}F FDG PET•CT is improving tumor definition dose escalation in non-small cell lung carcinoma by closely defining metastases and differentiating dead from thriving tissue. It offers valuable prognostic information on tumor volumes to plan the aggressiveness of radiation therapy, as well as assessing tumor response mid- and post-therapy.

By Percy Lee, MD, Department of Radiation Oncology, University of California Los Angeles, CA, USA, and Partha Ghosh, MD, Molecular Imaging, Siemens Healthcare, Hoffman Estates, IL, USA

Inside the disease

Lung cancer is the leading cause of cancer death globally. In 2007, in the United States alone, the annual incidence was 203,536, and some 158,683 died from lung cancer.[1] The overall 5-year survival of patients diagnosed with lung carcinoma is approximately 14%. Only one-third of presenting patients are eligible for curative-intent surgery.[2]
Radiation therapy (RT) plays a major role in patients who are not candidates for surgery. Recent advances in radiation therapy for non-small cell lung carcinoma (NSCLC), including intensity modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and stereotactic body radiotherapy (SBRT), have enabled higher radiation doses to be delivered to tumors for increased tumor local control, while reducing doses to surrounding normal tissue, thereby reducing radiation-induced short-term and long-term toxicities. Although CT-based planning is the standard approach, it only provides morphological information. Incorporating PET•CT with high volumetric resolution and accurate quantification into radiation treatment planning adds a layer of biological information that stand-alone CT does not provide. Improved targeting of viable tumor based on the delineation of the metabolically active tumor by Fludeoxyglucose F 18* (^{18}F FDG) PET•CT has been the basis of increased adoption of PET•CT based radiation therapy planning.



1 Centrally located left upper lobe tumor. ^{18}F FDG PET•CT shows large ^{18}FDG-avid mass without mediastinal metastases. Integrated contrast CT defines the relationship of the tumor with the adjacent aorta and pulmonary vessels. Automated 3D contouring of metabolically avid tumor performed using threshold of 40% of SUV_{max}. VOI exported as RT structure set for radiation planning.

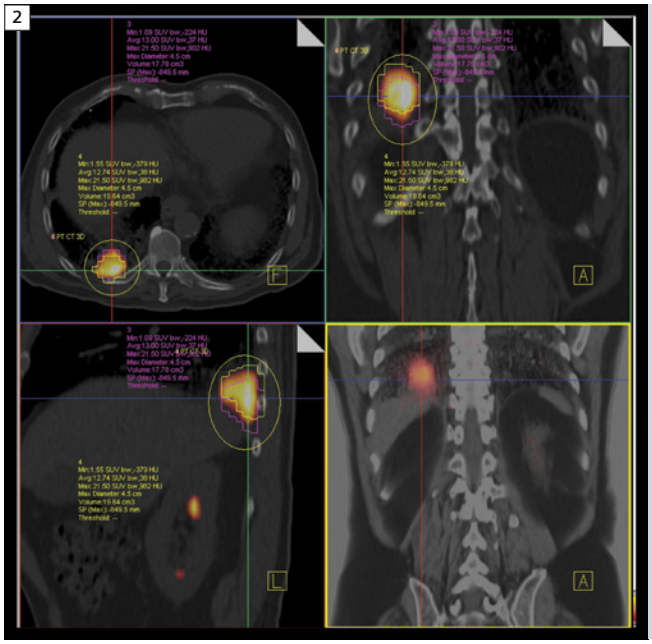
Staging with ^{18}F FDG PET•CT for Therapy Decision-making

^{18}F FDG PET•CT shows higher accuracy compared to CT alone for mediastinal and distant metastases and affects management for approximately one-third of patients.[3] Increased ^{18}F FDG uptake in metastatic nodes not enlarged by CT criteria is the reason for the heightened sensitivity of PET•CT, especially when using advanced scanners such as the Biograph™ mCT with the industry's highest volumetric resolution** of 87mm^3. PET•CT also is able to differentiate metabolically active lung tumor from atelectasis[4] and intratumoral necrotic zones, which helps better determine radiation therapy target volumes with the possibility to escalate dose to viable tumor, avoid radiation to normal tissue and reduce long-term fibrosis and related sequelae.[5]

Accurate detection of mediastinal lymph node metastases is critical for determining the application of SBRT for patients with early stage NSCLC. Li et al[6] in a multicenter study performed preoperative ^{18}F FDG PET•CT in 200 patients. The PET findings related to lymph nodes were confirmed with histopathological examination of the surgical specimen. PET•CT demonstrated high specificity (83%) and NPV (91%) for the presence of mediastinal lymph node metastases. The conclusion was that a negative PET•CT for mediastinal nodal metastases was sufficient evidence to justify treating the primary tumor with SBRT.

PET•CT can change the radiation field significantly by including ^{18}F FDG-avid non-enlarged metastatic lymph nodes within the treatment field. In view of the high negative predictive value of ^{18}F FDG PET•CT for nodal metastases (>90%), routine elective nodal radiation is no longer recommended.[7] It is proven to be safe to only irradiate PET positive lymph nodes, thus reducing target volume and resulting in a higher tumor dose.[8] Selective mediastinal lymph node irradiation based on PET with ^{18}F FDG yielded a low rate of treatment failure for isolated nodes, suggesting that reducing the target volume does not result in poorer local control.[5] This suggests that PET•CT-based IMRT would permit dose escalation with the avoidance of unnecessary elective nodal radiation.

^{18}F FDG PET•CT frequently changes disease stage by detecting unsuspected distant metastasis (>20% of pre-PET stage III), commonly in the liver, adrenal and bone, as well as identifying patients with very advanced locoregional (occult stage IIB-IIIB) disease[9] unsuitable for radical therapy. By upstaging patients with unsuspected metastases, PET•CT results in a lower rate of futile thoracotomies. In a large prospective trial, 30% of patients who were candidates for high-dose RT on the basis of conventional staging received only palliative therapies after PET because of unexpected distant metastasis (20%) or very extensive intrathoracic disease (10%).[10]



2 NSCLC at right lung base. ^{18}F FDG PET•CT shows hypermetabolic tumor mass close to diaphragm and posterior thoracic wall without nodal or distant metastases. Respiratory gated PET•CT was performed. Images show end inspiratory (pink) and end expiratory (yellow) metabolic tumor volumes superimposed on non-gated PET•CT image demonstrating tumor motion during the entire respiratory cycle.

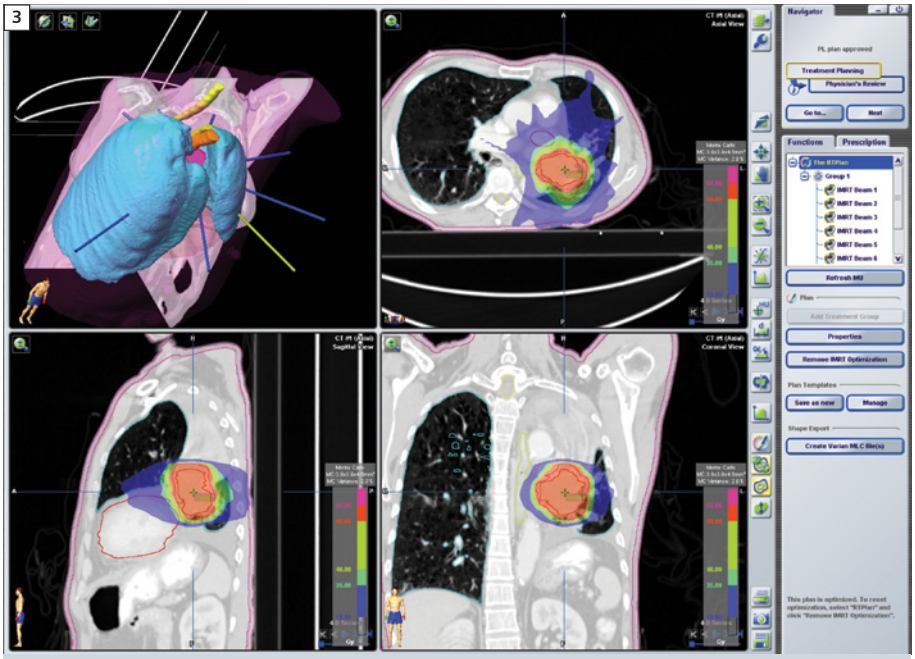
Delineating Tumor Volumes

Gross tumor volumes (GTVs) drawn based on hypermetabolic tumor have been shown to be significantly different from GTV drawn on CT only.[11] High-resolution Biograph mCT PET•CT-based planning offers the potential of dose escalation to the tumor regions with the highest ^{18}F FDG uptake in order to achieve improved local control and reduce local failure rates, as well as to help decrease radiation exposure of the lungs and the esophagus. In several planning studies, it was shown that GTV based on PET was in general smaller than with CT, thus leading to decreased radiation exposure of the lungs and the esophagus sufficiently as to allow for radiation-dose escalation.[12]

Meng et al[13] correlated microscopic extension of tumor on histopathology with SUV_{max} and GTV in NSCLC and found that microscopic extension is larger in tumors with higher SUV_{max}. The study suggested that margins of 1.93 mm, 3.90 mm and 9.60 mm for SUV_{max} ≤5, 5-10 and >10 added to the gross tumor volume would be adequate to cover 95% of microscopic tumor extensions.

PET•CT-based contouring for radiation therapy planning was compared to CT-based planning in 50 lung cancer patients who underwent radical RT.[14] Dosimetry target was to deliver 60 Gy in 30 fractions over 6 weeks. The study demonstrated that 37% of patients would have had a grade 1 geographic miss and 26% would have had a grade II geographic miss if RT was planned without PET. A grade 1 geographic miss is defined as inadequate GTV coverage, while a grade 2 geographic miss is defined as inadequate coverage of primary tumor value (PTV) excluding GTV.

The Radiation Therapy Oncology Group (RTOG) 0515 is a Phase II prospective trial designed to quantify the impact of PET•CT compared with CT alone on radiation treatment plans (RTPs) in NSCLC.[15] Forty-seven patients underwent ^{18}F FDG PET•CT followed by definite RT (>60Gy) based on a PET•CT-generated radiation plan. Mean follow-up was for 12.9 months. GTVs derived from PET•CT were significantly smaller than that from CT alone (Mean GTV volume 86.2 vs. 98.7 ml). PET•CT changed nodal GTV contours in 51% of patients. The elective nodal failure rate for GTVs derived by PET•CT was quite low, supporting the RTOG standard of limiting the target volume to the primary tumor and involved nodes. Mean lung dose using a PET•CT-based plan was slightly lower than that using CT, while there was no difference in mean esophageal dose.



3 Radiotherapy plan for the same patient with PTV (red) and CTV (green), as well as the V20 (magenta) delineated on CT. Patient received 50 Gy in 4 fractions of stereotactic body radiation therapy to the lung in May 2010. Early post-SBRT PET•CT imaging was performed in August 2010 to assess therapy response, which showed a complete metabolic response and re-inflation of the left lower lobe. Patient is free of local or distant recurrence or post-radiation complications to date with improved exercise tolerance and lowered oxygen usage. Courtesy of UCLA Medical Center SBRT program

Dose Escalation Based on SUV Thresholds

Local failure rates are high in NSCLC following radiation therapy. ^{18}F FDG PET•CT is able to determine high-risk tumors' subvolumes responsible for local failure, which may be subjected to dose escalation. However, levels of dose escalation are limited by the risk of complications. It has been demonstrated that areas with the highest ^{18}F FDG uptake in the pre-therapy scans are the sites with the highest potential for failure of local control and recurrence, thus selective boosting of tumor sub volumes with maximum ^{18}F FDG uptake is justified. Kong et al[16] performed ^{18}F FDG PET•CT in 14 patient with Stage I-III NSCLC before RT and in mid-RT (after 40-50 Gy). 3D conformal RT plans were generated for each patient, first using only pretreatment CT scans. Mid-RT PET volumes were then used to design boost fields. Mid-radiation therapy PET scan-based modification of radiation therapy plans allowed meaningful dose escalation of 30-102 Gy (mean 58 Gy) and a decrease in esophageal toxicity. There was a mean decrease in tumor volume after 40-50 Gy of 26% on CT and 44% on PET•CT. The study concluded that tumor metabolic activity and volume changes significantly after 40-50 Gy and adaptation of RT GTV based on mid-treatment PET•CT helps to escalate dose to active tumor, as well as reduce toxicity. In particular, PET•CT with high volumetric resolution and accurate quantification, such as the Biograph mCT, helps physicians to perform a precise dose escalation based on SUV thresholds.

Gated PET and CT-based Planning

Respiratory motion of lung tumor is a key factor that impacts radiation dose delivery to the tumor, as well as irradiation of normal lung tissue. Respiratory motion can be as large as 3 cm for lesions in lung bases. One study[17] reported that the range of tumor motion varied from 8 mm to 25 mm among five lung cancer patients. Respiratory motion assessment also can improve intratherapy modification of treatment plan to adopt to changes in tumor volume and motion during treatment fractions. Accurate estimation of motion and incorporation of such information into treatment planning is essential for SBRT and conventionally fractionated IMRT with dose escalation. Respiratory-correlated PET ameliorates motion blurring and enables visualization of lung tumor functional uptake throughout the breathing cycle.

Tumor volumes generated by 4D CT and respiratory gated PET were compared by Lamb et al[18] in four lower lobe lung tumors (4-18 cc in volume) in three patients. The GTV volumes generated by gated PET were on average 30% lower than those generated by 4D CT. Gated PET is particularly useful in lower lobe tumors with significant motion for SBRT planning and allows for more accurate representation of tumor motion than a 4D CT.

PET•CT-based Radiation Therapy Follow-up and Recurrence Detection

SUV_{max} changes during radiotherapy are significantly different between metabolic responders and non-responders. Metabolic responders have a better overall survival than the non-responders. Percentage decrease in SUV_{max} following RT directly correlates with disease-free survival.[19] Metabolic non-responders have been demonstrated to have a higher SUV_{max} at all time points investigated and showed a significant increase in SUV_{max} during the first week of irradiation followed by a decrease. In contrast, the responders showed a stable SUV_{max} during irradiation. The increase of SUV_{max} during the first week of RT was probably due to inflammation, since a rather high median dose of 19.8 Gy (1.8 Gy BID) was already delivered at the time point of the first repeat PET•CT scan. Sequential PET•CT imaging during radiation therapy has been shown to be beneficial for accurate evaluation of therapy response in spite of post-radiation

inflammation. Edet-Sanson et al[20] performed ^{18}F FDG PET•CT before and during radiation therapy (60-70 Gy, 2 Gy per fraction, 5 fractions per week) in 10 NSCLC patients. PET•CT was performed every 7 fractions (14 Gy total dose increments) with all patients undergoing 5 to 6 PET•CT studies. All 17 lesions (6 tumors and 11 nodal metastases) showed a progressive decrease in SUV_{max} with an increase in cumulative radiation dose. A 50% decrease in SUV_{max} was obtained around a total dose of 45-50 Gy (during week 5 of RT). ^{18}F FDG-PET images acquired during RT could be analyzed without disturbing radiation-induced artifacts.

Evaluating Response and Recurrence

^{18}F FDG PET•CT-based radiation therapy planning, particularly when performed with the latest scanner technology, such as the Biograph mCT with the highest volumetric resolution** and accurate quantification, for NSCLC can help to improve GTV definition and dose escalation by accurately defining mediastinal metastases and differentiating viable tumor from atelectasis and necrosis. PET•CT study prior to therapy provides valuable prognostic information from SUV, SUV_{max} and metabolic tumor volume that can help guide the aggressiveness of planned therapies. PET•CT-based radiotherapy planning assists in meaningful dose escalation without limiting increase in toxicity. Adaptive RT planning that uses mid-therapy PET•CT for modification of dose plan can achieve further dose escalation and improved local control. Sequential PET•CT imaging also has been shown to be valuable in evaluation of tumor response to radiation and recurrence detection. Current research with new biomarkers like proliferation and hypoxia agents shows further promise of incorporation of multiple metabolic information for improved dose planning and adaptive therapy in the future.

*Important safety information on Fludeoxyglucose F 18 injection can be found at right. The full prescribing information can be found on page 6.

** Based on competitive information available at time of publication. Data on file.

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Indications

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.
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- **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.

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

----------RECENT MAJOR CHANGES----------

Warnings and Precautions	(5.1, 5.2) 7/2010
Adverse Reactions	(6) 7/2010

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

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- Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures (1).

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

Fludeoxyglucose F18 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 F18 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 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 30mL and 50mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose F18 Injection and 4.5mg 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----------

- Pregnancy Category C: No human or animal data. Consider alternative diagnostics; use only if clearly needed (8.1).
- Nursing mothers: Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding (8.3).
- 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: 1/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fludeoxyglucose F18 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 F18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].

2.1 Recommended Dose for Adults

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

2.2 Recommended Dose for Pediatric Patients

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

2.3 Patient Preparation

- To minimize the radiation absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [see Warnings and Precautions (5.2)]. Prior to Fludeoxyglucose F 18 PET imaging in the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug's injection.
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F 18 Injection facilitates localization of cardiac ischemia

2.4 Radiation Dosimetry

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

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

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

a MIRDOSE 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Gallagher et al.1 and Jones et al.2

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 F18 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 F18 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 F18 Injection from its container.
- Inspect Fludeoxyglucose F18 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 30mL and 50mL 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 possibility of 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

Pregnancy Category C

Animal reproduction studies have not been conducted with Fludeoxyglucose F 18 Injection. It is also not known whether Fludeoxyglucose F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Consider alternative diagnostic tests in a pregnant woman; administer Fludeoxyglucose F 18 Injection only if clearly needed.

8.3 Nursing Mothers

It is not known whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in women who are breast-feeding. Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding.

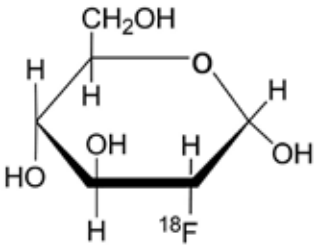
8.4 Pediatric Use

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

11 DESCRIPTION

11.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[^{18}F]fluoro-D-glucose has the molecular formula of 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 7.40GBq (20.0 to 200 mCi) of 2-deoxy-2-[^{18}F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

11.2 Physical Characteristics

Fluorine F 18 decays by emitting positron to Oxygen O 16 (stable) and has a physical half-life of 109.7 minutes. The principal photons useful for imaging are the dual 511 keV 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(ß+)	96.73	249.8 keV
Gamma(±)*	193.46	511.0 keV

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

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

Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding

Shield thickness (Pb) mm	Coefficient of attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

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

Table 4. Physical Decay Chart for Fluorine F 18

Minutes	Fraction Remaining
0*	1.000
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250

*calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

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

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

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

12.3 Pharmacokinetics

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

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

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Oncology

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

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

14.2 Cardiology

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

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

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

14.3 Neurology

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

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

15 REFERENCES

1. Gallagher B.M., Ansari A., Atkins H., Casella V., Christman D.R., Fowler J.S., Ido T., MacGregor R.R., Som P., Wan C.N., Wolf A.P., Kuhl D.E., and Reivich M. "Radiopharmaceuticals XXVII. 18F-labeled 2-deoxy-2-fluoro-d-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: tissue distribution and imaging studies in animals," J Nucl Med, 1977; 18, 990-6.
2. Jones S.C., Alavi, A., Christman D., Montanez, I., Wolf, A.P., and Reivich M. "The radiation dosimetry of 2 [F-18] fluoro-2-deoxy-D-glucose in man," J Nucl Med, 1982; 23, 613-617.
3. Kocher, D.C. "Radioactive Decay Tables: A handbook of decay data for application to radiation dosimetry and radiological assessments," 1981, DOE/TIC-I 1026, 89.
4. ICRP Publication 53, Volume 18, No. I-4,1987, pages 75-76.

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 7.40GBq/mL (20 to 200 mCi/mL), of no carrier added 2deoxy-2-[F 18] 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.

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