

# U.S. Medicare Reimbursement for PET

In 2013, the Centers for Medicare and Medicaid Services (CMS) issued a final decision memorandum on Positron Emission Tomography (PET) for Solid Tumors.<sup>1</sup> This decision memorandum was in response to the National Oncologic PET Registry's (NOPR) request to lift the requirement for Coverage with Evidence Development (CED) for NOPR-covered Fludeoxyglucose F 18 (<sup>18</sup>F FDG)\* PET indications on all subsequent PET scans for oncologic purposes. To confirm, there were three specific elements of this decision.

First, CMS ended the requirement for CED for <sup>18</sup>F FDG PET for oncologic indications. This removes the requirement for prospective data collection by the NOPR for cancers or cancer types that had been covered under CED. Second, CMS determined that, after completion of initial anti-cancer therapy, three <sup>18</sup>F

FDG PET scans are nationally covered when used to guide subsequent management of anti-tumor treatment strategy. Coverage of any additional <sup>18</sup>F FDG PET scans for subsequent management will be determined by local Medicare Administrative Contractors. Third, CMS will nationally cover <sup>18</sup>F FDG PET when it is used to guide subsequent anti-tumor treatment strategies of prostate cancer. (See chart below for more information regarding PET/CT indications and reimbursement.)

Effective for claims with dates of service on or after June 11, 2013, the National Coverage Determination allows and considers four <sup>18</sup>F FDG PET scans per patient per unique diagnosis when "medically necessary and appropriate." This includes one initial treatment strategy (ITS), formerly known as "diagnosis" and "staging"

and three subsequent treatment strategies (STS), formerly "restaging" and "monitoring response to treatment," for the same cancer diagnosis. Coverage for additional ITS and/or STS exams is determined and controlled by the regional Medical Administrative Contractors (MAC). MACs are not limiting reimbursement to three STS scans, but they require documentation of medical necessity for all STS PET scans beyond three. (For steps to appeal for reimbursement, see the "Five Levels of the Medicare Appeals Process" on page 2.)

#### References:

1. Final Decision Memorandum on Positron Emission Tomography (PET) for Solid Tumors (CAG-00191R4). (2013, June 11). Retrieved from <http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=263>

\* Indications and important safety information on Fludeoxyglucose F 18 Injection can be found on page 3. The full prescribing information can be found on pages 4-6.

The following table is taken from Appendix C of the National Coverage Determination for <sup>18</sup>F FDG PET/CT for oncologic conditions effective June 11, 2013.

Tumor Type	Initial Treatment Strategy	Subsequent Treatment Strategy
Colorectal	Covered	Covered
Esophagus	Covered	Covered
Head and Neck (not thyroid or CNS)	Covered	Covered
Lymphoma	Covered	Covered
Non-small cell lung	Covered	Covered
Ovary	Covered	Covered
Brain	Covered	Covered
Cervix	Covered with exceptions	Covered
Small cell lung	Covered	Covered
Soft tissue sarcoma	Covered	Covered
Pancreas	Covered	Covered
Testes	Covered	Covered
Prostate	Not covered	Covered
Thyroid	Covered	Covered
Breast (male and female)	Covered with exceptions	Covered
Melanoma	Covered with exceptions	Covered
All other solid tumors	Covered	Covered
Myeloma	Covered	Covered
All other cancers not listed	Covered	Covered

## Five Levels of the Medicare Appeals Process

Definition	Timing	Items to Include	Decision Notification	If You Are Dissatisfied with Notification
<b>Level 1: Request a Redetermination</b>				
An examination of a claim by Medicare contractor personnel who are different from the personnel who made the initial determination.	Within 120 days from the receipt of notice of the initial determination (Remittance Advice, "RA"). Notice of initial determination is presumed to be received five days from the date of the notice, unless evidence supports the contrary.	<p><b>Form CMS-20027:</b> <a href="http://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/CMS20027.pdf">http://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/CMS20027.pdf</a></p> <p>If the CMS-20027 form is not used, a written request must include: beneficiary name; Medicare Health Insurance Claim (HIC) number; service and/or item(s) for which a redetermination is requested; date(s) of service; name/signature of party or authorized/appointed representative; supporting documentation (e.g., referring physician's notes on why he/she referred the test in addition to the radiology report).</p>	Contractors generally issue a written Medicare Redetermination Notice (MRN) within 60 days of receiving the redetermination request.	Any party to the redetermination that is dissatisfied with the decision has 180 days to request a reconsideration (second-level appeal).
<b>Level 2: Reconsideration by Qualified Independent Contractor (QIC)</b>				
If dissatisfied with the requested redetermination, a party may request a reconsideration.	A written reconsideration request must be filed within 180 days of receiving the redetermination. A notice of the initial determination is presumed to be received five days from the date of the notice, unless evidence supports the contrary.	<p><b>Form CMS-20033:</b> <a href="http://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/CMS20033.pdf">http://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/CMS20033.pdf</a></p> <p>If the CMS-20033 form is not used, a written request must include: Medicare Health Insurance Claim (HIC) number; service(s) and/or item(s) for which the reconsideration is requested; date(s) of service; name and signature of party or authorized/appointed representative; name of contractor who made the redetermination; supporting documentation (e.g., all evidence for the appeal must be submitted at this level, unless good cause is shown; request should clearly explain the disagreement with the redetermination; a copy of the MRN and additional useful documentation).</p>	Within 60 days from the receipt of request for reconsideration, the QIC will, in most cases, send its decision to all parties. Reconsiderations are conducted "on the record."	Information for further appeals rights, including the process for requesting an Administrative Law Judge (third-level appeal), are detailed in the decision.
<b>Level 3: Hearing by an Administrative Law Judge (ALJ)</b>				
If at least 110 USD, a party may appeal for a Judicial Review in U.S. District Court by an ALJ.	A party to the reconsideration may request an ALJ hearing within 60 days of receiving the reconsideration.	Appellant must send a notice of the ALJ hearing request to all parties to the QIC reconsideration and verify this on the hearing or written request form. After providing notice, the CMS or its contractors may become a party to, or participate in, an ALJ hearing; case files are prepared by the QIC and forwarded to the Office of Medicare Hear & Appeals (OMHA); unless requested, no additional documentation is required.	The ALJ will generally issue a decision within 90 days of receiving the hearing request.	Details regarding procedures to follow when filing a request for Appeal Council Review are included within the ALJ's decision.
<b>Level 4: Medicare Appeals Council Review</b>				
If dissatisfied with the ALJ's decision, any party to the ALJ hearing may request a review by the Medicare Appeals Council. The Medicare Appeals Council reviews ALJ decisions on its own motion. There are no requirements regarding the amount of money in the controversy.	Within 60 days from the ALJ's decision or dismissal, the request for a Medicare Appeals Council review must be submitted in writing. The request must specify the issues and findings that are being contested.	Unless requested by the Medicare Appeals Council, no additional documentation is required.	The Appeals Council generally issues a decision within 90 days of receiving a request for review. This time frame may be extended for various reasons (e.g., the case being escalated from an ALJ hearing.)	If the Appeals Council does not issue a decision within the 90-day time frame, the appellant may ask the Medicare Appeals Council to escalate the case to the fifth level of appeal.
<b>Level 5: Federal Court Review</b>				
If 1,130 USD or more (based on 2007 threshold) is still in controversy after the Medicare Appeals Council's decision, a party to the decision may request judicial review before a U.S. District Court Judge.	The appellant must file the request for review within 60 days of receipt of the Appeals Council's decision.	Unless requested by the District Court Judge, no additional documentation is required.	Varies by case.	Varies by case.



## Fludeoxyglucose F18 5-10mCi as an IV injection

### Indications and Usage

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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

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- **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 on pages 4-6.

Fludeoxyglucose F 18 injection is manufactured by  
Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732



**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 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 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 F 18 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

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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 F18 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<sup>2</sup> data and using the data published by the International Commission on Radiological Protection<sup>4</sup> for Fludeoxyglucose <sup>18</sup>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\***

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 <sup>b</sup>	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

<sup>2</sup> 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

<sup>b</sup> 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 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.

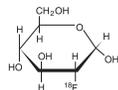
### 8.4 Pediatric Use

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-[<sup>18</sup>F]fluoro-D-glucose has the molecular formula of C<sub>6</sub>H<sub>11</sub><sup>18</sup>FO<sub>5</sub> 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-[<sup>18</sup>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).

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

\*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-1 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<sup>-6</sup> 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%.

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 [<sup>18</sup>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 condi-



tions, 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 [<sup>18</sup>F]-FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [<sup>18</sup>F]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[<sup>18</sup>F]fluoro-6-phospho-D-mannose([<sup>18</sup>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. Three elimination phases have been identified in the reviewed literature. 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 success-

ful 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 subphenoidal 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

- 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.
- Jones S.C., Alavi A., Christman D., Montanez I., Wolf, A.P., and Reivich M. "The radiation dosimetry of 2-[<sup>18</sup>F] fluoro-2-deoxy-D-glucose in man," *J Nucl Med*, 1982; 23, 613-617.
- Kocher, D.C. "Radioactive Decay Tables: A handbook of decay data for application to radiation dosimetry and radiological assessments," 1981, DOE/TIC-1 1026, 89.
- 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 7.40 GBq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-2-[<sup>18</sup>F] fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free. NDC 40028-511-30; 40028-511-50

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

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

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

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

## 17 PATIENT COUNSELING INFORMATION

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

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

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## PETNET Solutions

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