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.
Clinical Results

Case Study

**18F FDG*-PET•CT-based Radiation Therapy Planning and Follow-up in a Case of Carcinoma of the Base of the Tongue**

By Annika Loft Jakobsen, MD, Department of Nuclear Medicine, Rigshospitalet, Copenhagen, Denmark

**History**
A 44-year-old female patient presented with swelling on the left side of her neck, which was suggestive of an enlarged lymph node on clinical examination. The neck node was surgically removed and biopsy revealed metastases from squamous cell carcinoma. All clinical investigations including nasopharyngeal endoscopies were negative. In order to detect the primary tumor, the patient underwent Fluodeoxyglucose F 18 (18F FDG) PET•CT.

**Diagnosis**
An 18F FDG PET•CT scan was performed using a Biograph™ mCT, which is capable of high-resolution PET acquisition. High matrix reconstructions enabled by Hi-Rez acquisition and high count rate capability with ultraHD•PET on Biograph mCT enables excellent visualization of small metastatic lesions with high lesion contrast and low partial volume effect. The PET•CT study revealed a hypermetabolic primary tumor in the left side of the base of tongue.

Radiation planning was performed using the PET•CT data. SUV\(_{\text{max}}\) threshold-based tumor regions of interest (ROI) were contoured (Figure 2A) and exported to a radiation-treatment-planning system. The dose plan as shown (Figure 2B) delivered a high dose level to the primary tumor and the location of the initial lymph node.

**Comments**
The patient underwent radiation therapy according to the PET•CT-based dose escalation plan. A second PET•CT performed 3 months after the completion of radiotherapy showed no sign of residual or recurrent tumor.

This clinical example demonstrates the sensitivity of 18F FDG PET/CT for detection of primary tumor in patients presenting with malignant cervical nodal metastases from unknown primary. In a study of 38 consecutive patients with neck node metastases from unknown primary, Wartski et al found 18F FDG PET/CT positive in 68% of patients (26/38), which helped guide biopsies. PET/CT impacted treatment in 23 out of 38 patients (60%) including modification of radiation planning and surgery and in some cases cancellation of futile surgery.

**Examination Protocol**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scanner</strong></td>
<td>Biograph mCT 128</td>
</tr>
<tr>
<td>Scan dose</td>
<td>10 mCi (370 MBq) 18F FDG</td>
</tr>
<tr>
<td>Scan delay</td>
<td>1 hour post injection</td>
</tr>
<tr>
<td>Parameters</td>
<td>Whole body: 2 mininbed, Neck: single bed 5 min</td>
</tr>
<tr>
<td>Acquisition</td>
<td>400x400 matrix ultraHD•PET reconstruction</td>
</tr>
<tr>
<td>CT</td>
<td>130 kV, 70 eff mAs</td>
</tr>
</tbody>
</table>

18F FDG PET•CT axial section through the base of tongue shows a hypermetabolic primary tumor in the base of the tongue toward the left side. Note the free margins of the adjacent epiglottis. No clearly defined hypermetabolic lymph nodal metastases is delineated.
A recent meta-analysis involving 7 studies (246 patients) of the accuracy of 18F FDG PET and PET/CT in neck node metastases with unknown primary showed a sensitivity of 97%, but with a specificity of 68%.

PET/CT-based radiation therapy planning for oropharyngeal tumors has been widely adopted. High-matrix-resolution of PET acquisition along with improved lesion contrast provided by time-of-flight PET and point spread function (PSF) reconstruction have led to sharper delineation of tumor margins, as evident in this clinical example using Biograph mCT. Biograph mCT also incorporates a wide bore that supports radiation therapy planning with breast board and other immobilization devices. Dose escalation strategies based on PET uptake intensity have shown the potential for improving dose delivery to the target, while reducing toxicity to surrounding tissue and critical structures. Moreover, PET/CT-based metabolic imaging can be used as an effective follow-up tool after chemoradiation therapy. In a recent publication Chan et al, 77 patients with HPV-positive oropharyngeal squamous cell carcinoma underwent a follow-up 18F FDG PET/CT approximately 90 days after chemoradiation therapy. 18F FDG PET/CT with SUVmax threshold of 2 showed 100% negative predictive value compared to NPV of 85% shown by CT. Neck dissection was avoided in all patients negative on follow-up 18F FDG PET/CT with no regional failures after 6 months following PET/CT.

In the present study, a follow-up 18F FDG PET/CT was performed 3 months after completion of chemoradiation therapy and showed complete response of the primary tumor and no evidence of neck nodal metastases. The prognostic value of such findings is extremely positive. As demonstrated in this clinical example, 18F FDG PET/CT is an integral part of staging, therapy planning and follow up of oropharyngeal cancer.

References:
1. Nucl Med Commun. 2007 May;28(5):365-71
Fludeoxyglucose F 18 Injection, USP

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

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.
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.

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

1. 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).
2. In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 g) 2 to 3 hours prior to injection facilitates localization of cardiac ischemia (2.3).

**CONTRAINDICATIONS**
None

**WARNINGS AND PRECAUTIONS**
- Radiation risks: use smallest dose necessary for imaging (5.1).
- Glucose abnormalities: may cause suboptimal imaging (5.2).

**ADVERSE REACTIONS**
Adverse 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 fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**
Pregnancy Category: C

1.1 Adults

<table>
<thead>
<tr>
<th>Organ</th>
<th>Recommended Dose (mCi)</th>
<th>Actual Biodistribution</th>
<th>Estimated Absorbed Radiation Dose (rem/mCi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder wall</td>
<td>4.3</td>
<td>1.7</td>
<td>0.60</td>
</tr>
<tr>
<td>Heart wall</td>
<td>2.4</td>
<td>1.2</td>
<td>0.44</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.2</td>
<td>0.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.2</td>
<td>0.8</td>
<td>0.29</td>
</tr>
<tr>
<td>Liver</td>
<td>0.96</td>
<td>0.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.81</td>
<td>0.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.80</td>
<td>0.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.79</td>
<td>0.6</td>
<td>0.12</td>
</tr>
<tr>
<td>LLi wall*</td>
<td>0.69</td>
<td>0.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Liver</td>
<td>0.69</td>
<td>0.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Gallbladder wall</td>
<td>0.69</td>
<td>0.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.68</td>
<td>0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>LLi wall**</td>
<td>0.67</td>
<td>0.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.65</td>
<td>0.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.65</td>
<td>0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Testes</td>
<td>0.64</td>
<td>0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.62</td>
<td>0.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.61</td>
<td>0.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.61</td>
<td>0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.58</td>
<td>0.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Bone surface</td>
<td>0.57</td>
<td>0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Breast</td>
<td>0.54</td>
<td>0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Skin</td>
<td>0.49</td>
<td>0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Brain</td>
<td>0.29</td>
<td>0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Other tissues</td>
<td>0.59</td>
<td>0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 1. Estimated Absorbed Radiation Doses (rem/MCi) After Intravenous Administration of Fludeoxyglucose F-18 Injection

**REFERENCES**
Fludeoxyglucose F 18 Injection, USP

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 to authorize 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.
• 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.

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

5.1.2 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 to achieve a stable glucose level. In patients with Type 1 or Type 2 diabetes, consider safe and effective use of insulin to achieve adequate control of blood glucose levels for 3 to 5 days prior to imaging.

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.

6.3 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 radiology 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 C6H11F2O6 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-[18F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/v 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. Pricipal Radiation Emission Data for Fluorine F18

<table>
<thead>
<tr>
<th>Radiation/Emission</th>
<th>% Per Disintegration</th>
<th>Mean Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron (e+)</td>
<td>99.75</td>
<td>294.9 keV</td>
</tr>
<tr>
<td>Gamma (γ)</td>
<td>0.25</td>
<td>110.1 keV</td>
</tr>
</tbody>
</table>

*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-11026, 89 (1981)
The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 Rh/mC (1.35 x 10-6 GY/hrBq) 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

<table>
<thead>
<tr>
<th>Shield thickness (Pb) mm</th>
<th>Coefficient of attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>0.25</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
</tr>
<tr>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>8</td>
<td>0.001</td>
</tr>
<tr>
<td>10</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

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 F18

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>1.000</td>
</tr>
<tr>
<td>15</td>
<td>0.909</td>
</tr>
<tr>
<td>30</td>
<td>0.826</td>
</tr>
<tr>
<td>60</td>
<td>0.683</td>
</tr>
<tr>
<td>120</td>
<td>0.500</td>
</tr>
<tr>
<td>220</td>
<td>0.250</td>
</tr>
</tbody>
</table>

*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. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose F 18 transport and phosphorylation (expressed as the \textit{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.

The most significant metabolic and radiometabolic consequences of Fludeoxyglucose F 18 Injection are those involving uptake and utilization of the drug that is exogenously administered. 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-
Fludeoxyglucose F 18 Injection, USP

14.1 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 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


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 7.400 Gbq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-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 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.

Manufactured by: PETNET Solutions Inc.
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Knoxville, TN 37932

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