Combined $^{18}$F-FDG PET/MR for Enhanced Imaging of Active Cardiac Sarcoidosis

Nicolas A. Karakatsanis, Ph.D., MEng; Marc R. Dweck, M.D., Ph.D.; Ronan Abgral, M.D., Ph.D.; Maria Giovanna Trivieri, M.D., Ph.D.; Philip M. Robson, Ph.D.; Jason C. Kovacic, M.D., Ph.D.; Zahi A. Fayad, Ph.D.

Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Introduction

Sarcoidosis is a multisystem disease characterized by granuloma formation, inflammation and fibrosis most commonly affecting the lungs and mediastinal lymph nodes [1]. Cardiac involvement is under-diagnosed but is the leading cause of death amongst patients with sarcoidosis [2-6]. Early intervention with steroids appears to improve prognosis [7], making the accurate and early diagnosis of subclinical but active cardiac sarcoidosis an important clinical goal. Unfortunately establishing this important diagnosis remains a major clinical challenge [8, 9].

Cardiac magnetic resonance (MR) imaging with late gadolinium enhancement (LGE) has recently been introduced for visualizing the pattern of myocardial injury due to cardiac sarcoidosis [10, 11]. However, LGE cannot differentiate between active disease and old chronic scarring, thus limiting the specificity of CMR-based active sarcoidosis assessments. On the other hand, positron emission tomography (PET) imaging with $^{18}$F-Fludeoxyglucose ($^{18}$F-FDG), a glucose analog and radiotracer widely used to assess the inflammatory response, has recently been used to identify regions of increased myocardial inflammation in patients with active cardiac sarcoidosis [12-14]. However, glucose is the predominant source of energy consumed by the myocardium, and high non-specific physiological uptake of $^{18}$F-FDG can often lead to false positive identification of active myocardial disease. Although dietary restrictions in the 12 hours prior to PET imaging may switch the heart from glucose to free-fatty acid metabolism and effectively suppress physiological $^{18}$F-FDG uptake in the myocardium, this strategy is not always successful [14-16].

Recently, hybrid PET/MR systems have become clinically available [17-19]. The simultaneous hybrid PET/MR Biograph mMR system (Siemens Healthcare, Erlangen, Germany) combines a sensitive PET scanner with a 3T MR system to enable spatial co-registration of complementary imaging data from the two modalities [20]. Simultaneous acquisition of PET and MR data allows disease activity measured by PET to be precisely overlaid on the pattern of injury in the myocardium determined by MR from a single scan session [21]. Moreover, by replacing CT with MR, PET/MR is associated with a lower radiation dose, which is important, especially in chronic conditions such as cardiac sarcoidosis, where follow up would be desirable [17].

Recent studies in our institution have investigated the use of MR/PET for evaluating cardiac disease [21, 22] including cardiac sarcoidosis by assessing the overlap between $^{18}$F-FDG-PET activity and the pattern of myocardial injury on LGE MR. We have investigated the potential of combined PET/MR to differentiate between active and inactive cardiac sarcoid as well as identifying false-positive PET indications.

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1 The full prescribing information for the Fludeoxyglucose F18 injection can be found at page XX.

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**Figure 1:** From left to right: (1A, C) LGE MR images showed elevated LGE signal at the lateral and anteroseptal wall for patient 1 (62-year-old male) and patient 2 (63-year-old female) respectively. (1B, D) Matched $^{18}$F-FDG PET fused with previous LGE MR images showed high $^{18}$F-FDG uptake overlapping with the LGE pattern of injury.
due to inadequate physiological $^{18}$F-FDG myocardial uptake suppression [22, 23].

**Optimized PET/MR imaging protocol for cardiac sarcoidosis assessment**

In this article, we present four clinical exams where initial diagnosis for active cardiac sarcoidosis was unclear when either LGE MR or $^{18}$F-FDG PET exams were evaluated independently [22, 23]. All participating subjects had a previous history of proven extra-cardiac sarcoidosis and/or clinical symptoms to suggest cardiac sarcoid involvement. Patients gave written informed consent and were screened for contra-indications before undergoing PET/MR imaging.

Dynamic PET data were acquired across a single bed position centered over the heart in list mode for a period of 90 min beginning 10 min after 5 MBq/kg $^{18}$F-FDG injection. The collected PET data were then histogrammed into a single scan time window corresponding to a delayed 40-100 min post-injection period. Subsequently the PET data were reconstructed with an iterative ordinary Poisson ordered subset expectation maximization (OP-OSEM) algorithm using 3 iterations, 21 subsets and a resolution modeling method optimized for the Biograph mMR system. An MR-based attenuation correction method was employed for the PET data based on 4-tissue class segmentation of a standard breath-hold 3D Dixon-VIBE MR sequence. Attenuation from the body transmit coil and spine array, but not from the flexible chest array, were included in the attenuation map.

Cardiac MR, performed simultaneously with the dynamic PET acquisition, included

- i) TrueFISP cine images, acquired in the long-axis (2-chamber, 4-chamber) of the left ventricle, followed by
- ii) a complete short-axis stack for assessment of cardiac volume and function, and
- iii) inversion recovery-prepared spoiled gradient echo late gadolinium enhanced imaging, 10-15 minutes post injection of 0.2 mmol/kg Multi Hance (Bracco imaging, Milan, Italy) in short- and long-axis views [24]. Inversion times were optimized to null normal myocardium with images repeated in two separate phase-encoding directions to exclude artifact.

**Enhancing cardiac sarcoïd diagnosis with simultaneous MR/PET imaging**

In patients 1 and 2, elevated $^{18}$F-FDG uptake (at later times >60 min post tracer injection) co-localized with the pattern of late gadolinium enhancement observed on MR (Fig. 1). The coincidental observation of both increased FDG-PET activity and evidence of myocardial injury on late gadolinium enhancement strongly suggests the presence of active cardiac sarcoïdosis. TBR values were calculated as mean standard uptake values (SUV) in regions-of-interest (ROI) drawn over the area of myocardial injury divided by the mean blood pool SUV value in the left ventricular cavity. Mean $^{18}$F-FDG target-to-background (TBR) in areas of myocardial injury were 2.2 (patient 1) and 2.0 (patient 2).

Conversely, overlap of PET and LGE was not observed in patients 3 and 4 (Fig. 2). In patient 3 (first row) transmural scarring in a coronary distribution affecting the anteroseptum was observed on LGE MR but with no evidence of increased $^{18}$F-FDG PET uptake in this region. This finding was felt to be consistent with a chronic and silent myocardial infarction. By contrast, patient 4 demonstrated avid and diffuse $^{18}$F-FDG uptake throughout the entire left ventricular myocardium in the absence of any evidence of myocardial injury on LGE MR. Given that cardiac sarcoïdosis is a focal disease process this was felt likely to represent failed suppression of the physiological $^{18}$F-FDG uptake [25]. This hypothesis was supported by the very high TBR values (6.3 60-90 min post injection) in this patient compared to subjects 1 and 2. However, more evidence is needed to be able to differentiate the true- from the false-positive cardiac sarcoïd $^{18}$F-FDG assessments in the absence of positive LGE MR signal.

**Future prospects for cardiac PET/MR imaging**

This preliminary study has demonstrated the clinical potential of simultaneous MR/PET imaging in the evaluation of active cardiac sarcoïdosis. PET and MR images

Figure 2: (2A, B) Patient 3 (50-year-old female), short-axis LGE MR showed transmural LGE on the anteroseptum, while fused MR/PET images demonstrated absence of high $^{18}$F-FDG uptake on the same region. (2C, D) Patient 4 (42-year-old male) LGE MR showed absence of LGE on the myocardial wall. Fused MR/PET images indicated diffused intense $^{18}$F-FDG uptake.
can be accurately aligned allowing a diagnosis of active cardiac sarcoidosis to be made with confidence when increased 18F-FDG uptake co-localizes with the pattern of injury on late gadolinium enhancement MR. Moreover this approach can help differentiate this pattern from non-active cardiac sarcoid LGE signal or false positive 18F-FDG uptake due to failed myocardial suppression.

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

1.1 Oncology
For the identification of regions of abnormal glucose metabolism associated with foci of malignant disease.

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.

Dosage and Administration

Fludeoxyglucose F 18 Injection is given as an intravenous injection (2).

Use of Radiating Materials

Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

1. In the oncology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection.

2. In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection.

3. In the neurology 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 (2.3).

4. Consider patient preparation with MIRDose 2 software to calculate the radiation absorbed dose. Assumptions on body size were made based on human data and using the data published by the International Commission on Radiological Protection for Fludeoxyglucose F 18 injection. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These variations 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 Doses (rem/mCi) After Intravenous Administration of Fludeoxyglucose F 18 Injection

<table>
<thead>
<tr>
<th>Organ</th>
<th>Newborn</th>
<th>1-year old</th>
<th>5-year old</th>
<th>10-year old</th>
<th>15-year old</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder wall</td>
<td>4.1</td>
<td>1.7</td>
<td>0.93</td>
<td>0.60</td>
<td>0.46</td>
<td>0.32</td>
</tr>
<tr>
<td>Heart wall</td>
<td>2.6</td>
<td>1.2</td>
<td>0.70</td>
<td>0.44</td>
<td>0.29</td>
<td>0.22</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.2</td>
<td>0.68</td>
<td>0.33</td>
<td>0.25</td>
<td>0.13</td>
<td>0.096</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.2</td>
<td>0.84</td>
<td>0.46</td>
<td>0.29</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.96</td>
<td>0.38</td>
<td>0.20</td>
<td>0.13</td>
<td>0.092</td>
<td>0.044</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.81</td>
<td>0.34</td>
<td>0.19</td>
<td>0.13</td>
<td>0.049</td>
<td>0.076</td>
</tr>
<tr>
<td>Ovariies</td>
<td>0.80</td>
<td>0.38</td>
<td>0.20</td>
<td>0.13</td>
<td>0.049</td>
<td>0.076</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.79</td>
<td>0.35</td>
<td>0.19</td>
<td>0.12</td>
<td>0.076</td>
<td>0.062</td>
</tr>
<tr>
<td>LLI wall</td>
<td>0.69</td>
<td>0.28</td>
<td>0.15</td>
<td>0.097</td>
<td>0.060</td>
<td>0.051</td>
</tr>
<tr>
<td>Liver</td>
<td>0.69</td>
<td>0.31</td>
<td>0.17</td>
<td>0.11</td>
<td>0.076</td>
<td>0.058</td>
</tr>
<tr>
<td>Gallbladder wall</td>
<td>0.69</td>
<td>0.26</td>
<td>0.14</td>
<td>0.093</td>
<td>0.059</td>
<td>0.049</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.68</td>
<td>0.29</td>
<td>0.15</td>
<td>0.096</td>
<td>0.060</td>
<td>0.047</td>
</tr>
<tr>
<td>ULI wall</td>
<td>0.67</td>
<td>0.27</td>
<td>0.15</td>
<td>0.090</td>
<td>0.057</td>
<td>0.046</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.65</td>
<td>0.27</td>
<td>0.14</td>
<td>0.089</td>
<td>0.057</td>
<td>0.047</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.65</td>
<td>0.28</td>
<td>0.15</td>
<td>0.095</td>
<td>0.061</td>
<td>0.048</td>
</tr>
<tr>
<td>Testes</td>
<td>0.64</td>
<td>0.27</td>
<td>0.14</td>
<td>0.085</td>
<td>0.052</td>
<td>0.043</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.62</td>
<td>0.26</td>
<td>0.14</td>
<td>0.089</td>
<td>0.057</td>
<td>0.047</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.61</td>
<td>0.26</td>
<td>0.14</td>
<td>0.086</td>
<td>0.056</td>
<td>0.044</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.61</td>
<td>0.26</td>
<td>0.13</td>
<td>0.080</td>
<td>0.049</td>
<td>0.039</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.48</td>
<td>0.20</td>
<td>0.13</td>
<td>0.079</td>
<td>0.049</td>
<td>0.039</td>
</tr>
<tr>
<td>Bone surface</td>
<td>0.57</td>
<td>0.24</td>
<td>0.12</td>
<td>0.079</td>
<td>0.052</td>
<td>0.044</td>
</tr>
<tr>
<td>Breast</td>
<td>0.54</td>
<td>0.22</td>
<td>0.11</td>
<td>0.068</td>
<td>0.043</td>
<td>0.034</td>
</tr>
<tr>
<td>Skin</td>
<td>0.49</td>
<td>0.20</td>
<td>0.10</td>
<td>0.060</td>
<td>0.037</td>
<td>0.030</td>
</tr>
<tr>
<td>Brain</td>
<td>0.29</td>
<td>0.13</td>
<td>0.09</td>
<td>0.078</td>
<td>0.072</td>
<td>0.070</td>
</tr>
<tr>
<td>Other tissues</td>
<td>0.59</td>
<td>0.25</td>
<td>0.13</td>
<td>0.083</td>
<td>0.052</td>
<td>0.042</td>
</tr>
</tbody>
</table>

* MIRDose 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Hall et al. and Jones et al. 2
* 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.
- Radioisotopes 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 time of synthesis (EOS) time using proper radioactive decay factors. Assume the final dose in a properly calibrated dose calibrator before administration to the patient (see Description [11.2]).
- Do not administer the drug if it contains particulate matter or discoloration; dispose of the unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.

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 the unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.

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 DOSE FORMS AND STRENGTHS

Fludeoxyglucose F 18 Injection is a multiple-dose glass vial and does not contain any preservative. 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.

3.1 Radiation Risks

Fludeoxyglucose F 18 Injection may increase the risk of 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]).

3.2 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.

4 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.

5 DRUG INTERACTIONS

The possibility of interactions of Fludeoxyglucose F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

6 USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

There is a lack of evidence to determine whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in a pregnant woman who is 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.

6.2 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 mg/kg. 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.

7 DRUG DISSOLUTION

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

Animal reproduction studies have not been conducted with Fludeoxyglucose F 18 Injection. Do not administer Fludeoxyglucose F 18 Injection to a woman who is breast-feeding.

8.2 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.

8.3 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 mg/kg. 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.

10 DESCRIPTION

10.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a position-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 C₈H₁₄O₆F with a molecular weight of 181.26, and has the following chemical structure:

![Chemical structure of 2-[18F]FDG](image)

Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.76g to 7.40gBq (20 to 200 mCi) of 2-deoxy-2-[18F]fluoro-d-glucose at the EOS, 4.5 mg of sodium chloride, and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose vial and does not contain any preservative.

11 PHYSICAL CHARACTERISTICS

Fludeoxyglucose F 18 Injection decays by emitting positron to Oxygen 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).

2. Characteristics of 2-[18F]FDG

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight</td>
<td>181.26</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td><img src="image" alt="image" /></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 3. Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

<table>
<thead>
<tr>
<th>Shielding Thickness (in)</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
</tr>
<tr>
<td>8</td>
<td>0.25</td>
</tr>
<tr>
<td>12</td>
<td>0.10</td>
</tr>
<tr>
<td>16</td>
<td>0.03</td>
</tr>
<tr>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>26</td>
<td>0.001</td>
</tr>
<tr>
<td>32</td>
<td>0.0001</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 facilitated 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.

In the oncology and neurology setting, 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 Pharmacokinetics

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 increase rate of phosphorylation activity, (3) a reduction of phosphatase activity, and (4) a dynamic change 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 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 glucose metabolism of the brain after a seizure is decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

12.3 Pharmacokinetics

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 2.87 x 10^-4 (2.87 x 10^-4 R/hr/mCi) at 1 m. The half-value layer (HVL) for the single photon is summarized in Table 2. The range of attenuation coefficients for this radionuclide as a function of lead shield thickness is shown in Table 3. For example, the intersection of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.
Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose [CDG]). Biodegradation and metabolism of CDG 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 (CDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (CDM-6-phosphate). The phosphorylated deoxyglucopyranosyl compounds are dephosphorylated and the resulting compounds, FDM, CDG, and CDM, are then further metabolized and excreted via the urine.

Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 2 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 unchanged by the renal system. 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 medically-impaired, heparin-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, colon-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin’s and non-Hodgkin’s lymphomas, 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 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. The degree of myocardial segmental recovery of systolic function 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 56% (44/87) of the patients; in 34% (30/87) of the patients, Fludeoxyglucose F 18 Injection PET imaging 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 subependymal EGI, MRI and/or surgical findings support 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 diaphasic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

15 REFERENCES
4. ICRP Publication 53, Volume 18, No. 1-4-1987: 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 0.74 to 7.40 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.

Flight risk: No need for airline clearance; however, for international flights, clearance should be obtained.

Repossession, 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 the 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 time of dosing.

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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830 Innovation Drive
Knoxville, TN 37932

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