Hybrid PET/MR Imaging with PSMA-Ligands: the Future Standard in the Diagnosis of Prostate Cancer?

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Prostate cancer (PCa) is the most frequent malignant tumor in men worldwide [1, 2]. Following initial therapy, mostly by surgery or radiation, biochemical relapse is rather common [3–6]. The search for tumor lesions at this constellation is challenging, since imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) often revealed unsatisfying sensitivity and specificity [7].

Research has therefore sought to find more sensitive and specific ways of diagnostic measures. The fact that prostate-specific membrane antigen (PSMA) is known to be overexpressed in most PCa offers the chance to develop ligands for this target. This has led to the introduction of the low-molecular-weight PSMA-ligand Glu-NH-CO-NH-Lys-(Ahx)-[^68Ga(HBED-CC)] (= ^68Ga-PSMA-11) in 2011 as a novel PET-tracer for diagnosing PCa. This compound was developed at the German Cancer Research Center Heidelberg, Germany [8, 9]. The first clinical application of ^68Ga-PSMA-11-PET/CT was conducted in May 2011 in the department of nuclear medicine at the Heidelberg University Hospital. This led to the rapid international spread of this novel imaging method. The growth can be explained by the hitherto existing results of PET/CT-imaging with ^68Ga-PSMA-11, which clearly demonstrate a significant increase in the diagnostic capabilities for the detection of PCa-related tissue [10–13]. A recently published study with a large patient cohort (n = 319) affirmed that ^68Ga-PSMA-11-PET/CT provides excellent sensitivity and specificity to detect PCa lesions [12]. Other groups have confirmed these findings [14].

When compared to CT, MRI provides a better method of soft tissue imaging due to its higher contrast-resolution and different functional sequences, both helping to clarify uncertain findings. Multiparametric MRI of the prostate has been proven as a powerful imaging tool for prostate cancer assessment [15]. It provides essential information for accurate prostate biopsy using TRUS/MR image-fusion guided biopsy systems, and is an integral part of follow-up during active surveillance and individualized therapy planning [16]. However, there are significant limitations in the early detection of cancer spreading into lymph nodes and bones, or of recurrent disease after curative intended treatment. These limitations can be overcome by adding the information from PSMA-PET, which yields complementary information compared to multiparametric MR. Consequently, the next step should therefore be a combination of PSMA-PET with MRI,
thus creating the best possible tool to detect, diagnose, stage and follow-up patients with suspected prostate cancer comprehensively and most accurately within ‘one-stop-shopping’.

Siemens is the first company to have successfully developed a hybrid whole-body PET/MRI scanner allowing for simultaneous PET and MRI assessment. The objective of such hybrid scanners is a faster investigation and more accurate image fusion compared to separately conducted PET and MRI images.

As dedicated software to fuse separately acquired PET and MRI images already exists, some experts may argue that the development of hybrid PET/MRI scanners was a bit futile. Bearing in mind that very similar arguments were raised at the time of hybrid PET/CT scanner development, the ensuing years have clearly showed multiple advantages of those scanners: the image fusion was found to be more accurate when compared to the images that were reconstructed based on retroactive fusion of separately obtained PET and CT/MRI images. Human errors in the context of image fusion could also be avoided as no manipulation by humans is required. All this has resulted in saved time and resources. Furthermore, with regard to external radiation therapy, the development of hybrid PET/CT has enabled more accurate therapy approaches. In addition, PET/MRI allows parallel acquisition of PET and MRI, whereas for PET/CT the scans have to be conducted sequentially. At last, patients who undergo a PET/MRI scan are also exposed to less radiation compared to PET/CT.

After the development of hybrid whole-body PET/MRI scanners, multiple studies have been published which demonstrate the feasibility and the advantages of a PET/MRI hybrid system when using $^{18}$F-FDG or $^{18}$F-Choline. In 2013, our group began conducting PET/MRI with $^{68}$Ga-PSMA-11 and the results were highly promising [9-12]. In fact, a subjectively easier evaluation of the images compared to PET/CT could be shown; an effect enabled by different diagnostic sequences and the higher resolution of MRI. The combination of the $^{68}$Ga-PSMA-11-PET with multiparametric MRI provided images of a high diagnostic value not witnessed before (Figs. 1, 2). MRI has also helped to clarify unclear findings in PET/CT regarding PCa metastases (Fig. 3). The appearance of a reduced PET-signal around the urinary bladder in some patients was the only noticeable limitation compared to PET/CT [12]. However, there are strategies for reducing or even omitting the described effect, i.e. a sufficient hydration of the patients, voiding the bladder prior to acquisition and starting the examination with the pelvis when the bladder is less full. Further, a newly developed software offering two different types of scatter correction (relative and absolute scatter correction) can help to significantly reduce the described effect.

In summary, the authors strongly believe that hybrid $^{68}$Ga-PSMA-PET/MRI has significant advantages over PET/CT and will create new options for the diagnosis and selective treatment of primary and recurrent PCa in the future.

Acknowledgements

We express our gratitude to our staff, in particular to Regula Gnirs, René Hertel and Dr. Henrik Hetzheim.

Some of the Imaging Biomarkers referenced herein are not currently recognized by the US FDA as being safe and effective, and Siemens does not make any claims regarding their use. The statements by Siemens’ customers described herein are based on results that were achieved in the customer’s unique setting. Since there is no ‘typical’ hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

References


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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fludeoxyglucose F 18 Injection safely and effectively. See full prescribing information for Fludeoxyglucose F 18 Injection. Fludeoxyglucose F 18 Injection, USP For intravenous use

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

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.

DOSE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. See screen for blood glucose abnormalities (2.2).

In the oncology 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.

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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Newborn (77.5 cm)</th>
<th>1-year old (77.5 cm)</th>
<th>5-year old (101.6 cm)</th>
<th>10-year old (125.7 cm)</th>
<th>15-year old (149.9 cm)</th>
<th>Adult (174.0 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder wall</td>
<td>4.3</td>
<td>1.7</td>
<td>0.93</td>
<td>0.60</td>
<td>0.40</td>
<td>0.32</td>
</tr>
<tr>
<td>Heart wall</td>
<td>2.4</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>0.14</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>0.064</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.81</td>
<td>0.34</td>
<td>0.19</td>
<td>0.13</td>
<td>0.089</td>
<td>0.074</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.80</td>
<td>0.8</td>
<td>0.19</td>
<td>0.11</td>
<td>0.058</td>
<td>0.053</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>0.041</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>Muscles</td>
<td>0.58</td>
<td>0.25</td>
<td>0.13</td>
<td>0.078</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>0.041</td>
</tr>
<tr>
<td>Breast</td>
<td>0.54</td>
<td>0.22</td>
<td>0.11</td>
<td>0.064</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>

* MIRD/2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution were made from data of Gallagher et al. 1 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

1.1 Oncology

For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

1.2 Cardiology

For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

1.3 Neurology

For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

2 DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Adjust 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 data and using the data published by the International Commission on Radiological Protection for Fludeoxyglucose F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each age group. 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 were the urinary bladder, heart, pancreas, spleen, and lungs.

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

- 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 (8.3).

ADVERSE REACTIONS

- Radiation risks: use smallest dose necessary for imaging (5.1).
- Blood glucose abnormalities: may cause suboptimal imaging (5.2).

ADVERSE REACTIONS

Hyperosmolar 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.
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.
• Radiopharmacists 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.
• Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.
• Do not administer the drug if it contains particulate matter or discoloration; dispose of.
• 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 Patients Undergoing PET Imaging
• 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.

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

11 DESCRIPTION
11.1 Chemical Characteristics
Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[18F]fluoro-D-glucose has the molecular formula of C6H11FO6 with a molecular weight of 181.26, and has the following chemical structure:

\[
\text{O} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{F}
\]

Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.400 GBq (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 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 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 (β+)</td>
<td>96.73</td>
<td>249.8 keV</td>
</tr>
<tr>
<td>Gamma (γ)*</td>
<td>193.46</td>
<td>511.0 keV</td>
</tr>
</tbody>
</table>

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

The specific gamma ray constant (point-source air kerma coefficient) for fluorine F 18 is 5.789 mR/ h/mCi (0.35 x 10.6 Ghry/mCi) 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 interpolation 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>4</td>
<td>0.50</td>
</tr>
<tr>
<td>8</td>
<td>0.25</td>
</tr>
<tr>
<td>13</td>
<td>0.10</td>
</tr>
<tr>
<td>26</td>
<td>0.01</td>
</tr>
<tr>
<td>39</td>
<td>0.001</td>
</tr>
<tr>
<td>52</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 administration 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>110</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 ‘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 myocardium is metabolized immediately instead of being converted into glycogen. Under these conditions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocardium 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.

13.3 Pharmacokinetics

Distribution: In four healthy male volunteers, receiving an intravenous administration of 30 seconds in duration, the arterial blood level profile for Fludeoxyglucose F was 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 (STDEV) of 11.6 ± 1.1 min, and 80 to 95 minutes with a mean and STDEV of 88 ± 4 min. Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

Metabolism: Fludeoxyglucose F 18 is transported to cells and phosphorylated to [18F]FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [18F]FDG-6-phosphate is metabolized to 2-deoxy-2-[18F]fluoro-6-phospho-D-mannose (FDMP-6-phosphate) and 2-deoxy-2-[18F]fluoro-6-phospho-D-mannose (CDMP-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDMP, CDIM, and CDIM) 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 have not been studied in renal-impaired, heparinically 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, colorectal, pancreatic, breast, thyroid, melanoma, Hodgkin’s and non-Hodgkin’s lymphoma, and various types of metastatic cancers to lung, including non-small cell lung cancer, colorectal, pancreatic, breast, thyroid, melanoma, Hodgkin’s and non-Hodgkin’s lymphoma, and various types of metastatic cancers to lung.

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 mc). 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 focs 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 subependural EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foco. The safety and carcinogenicity of Fludeoxyglucose F 18 was established; no evidence of carcinogenic foci from tumors or other brain lesions that may cause seizures has not been established.

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND 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 mcL/mL), of no carrier added 2-deoxy-2-[18F] fluoride-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 (± 15°C); excursions permitted to 10°C to 30°C (± 5°C). 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.

Manufactured by: PETNET Solutions Inc.
810 Innovation Drive
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Distributed by: PETNET Solutions Inc.
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Indications

Fludeoxyglucose F18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

• Oncology: For the staging of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

• Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

• Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

Important Safety Information

• Radiation Risks: Radiation-emitting products, including Fludeoxyglucose F18 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 healthcare 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/or laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F18 Injection administration.

• Adverse Reactions: Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available.