18F FES PET/CT imaging in recurrent metastatic invasive lobular breast cancer

By Kritika Subramanian, MD,1 Dunya Imad, MD,1 Ryan Pereira, CNMT,1 Lady Sawoszczyk, CNMT,1 Joseph Osborne, MD, PhD,1 Eleni Andreopoulou, MD,2 and Trisha Youn, MD1

Data and images courtesy of NewYork-Presbyterian Hospital / Weill Cornell Medical Center, New York, NY, USA

History

A 75-year-old female with recurrent, metastatic, invasive lobular breast cancer—8 years post-diagnosis and also in remission for lymphoma—underwent routine Fludeoxyglucose F 18 (18F FDG) Injection[a] PET/CT imaging to evaluate disease progression. Two years prior, the patient had completed 5 years of letrozole therapy for the initial breast cancer diagnosis.

Routine 18F FDG PET/CT findings indicated diffuse 18F FDG-avidity throughout the osseous structures as well as sclerotic osseous lesions without 18F FDG-avidity above the remainder of marrow. A pelvic bone biopsy demonstrated metastatic breast cancer that was >99% estrogen receptor (ER) positive and 80% progesterone receptor (PR) positive. Subsequent treatment therapy included aromatase inhibitors (AIs), cyclin-dependent kinase (CDK4/6) inhibitors, and nuclear factor kappa-B ligand (RANKL) inhibitors.

The patient returned for a 1-year follow-up evaluation to help determine the extent of ER-positive osseous lesions. For the initial PET/CT, the patient was administered with 10.7 mCi (396 MBq) intravenous (IV) injection of 18F FDG, and approximately 1 hour later, a single-scan, whole-body acquisition was conducted on a Biograph mCT FlowTM system.

Two weeks later, the patient underwent a PET/CT using CeriannaTm (Fluoroestradiol F 18 [18F FES]) Injection[b], a PET imaging agent for use in recurrent or metastatic ER-positive breast cancer as an adjunct to biopsy (Cerianna NDA holder is Zionexa). The patient was administered with 5.5 mCi (202 MBq) IV injection of 18F FES, and approximately 80 minutes later, a single-scan, whole-body acquisition was conducted on a Biograph mCT FlowTM system.
**Fludeoxyglucose F 18 Injection**

**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.

**IMPORTANT SAFETY INFORMATION**

- **Radiation Risks:** Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker.
- **Blood Glucose Abnormalities:** In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.
- **Adverse Reactions:** Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available.

**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.

Fludeoxyglucose F 18 Injection is manufactured by PETNET Solutions, a Siemens Healthineers Company, 810 Innovation Drive, Knoxville, TN 39732.
CERIANNA™ (fluoroestradiol F 18) Injection

INDICATIONS AND USAGE
• ^18F-FES is a radioactive diagnostic agent indicated for PET imaging.
• ^18F-FES is indicated for the detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.

Limitations of use
• Tissue biopsy should be used to confirm recurrence of breast cancer and to verify ER status by pathology. ^18F-FES is not useful for imaging other receptors, such as HER2 and PR.

IMPORTANT SAFETY INFORMATION
• Adverse Reactions: Reported adverse reactions include: injection site pain and dysgeusia.
• Radiation Risks: Ensure safe drug handling and patient preparation procedures to protect patients and health care providers from unintentional radiation exposure.
• Risk of Misdiagnosis: Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer.
• Contraindications: None.
• Use in specific populations: Lactation – Interrupt breastfeeding. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration.

To report SUSPECTED ADVERSE REACTIONS, contact Zionexa US Corp at +1.844.946.6392 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION
Dosage form and strengths
• Injection: clear, colorless solution in a multiple-dose vial containing 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of Cerianna at end of synthesis.

Patient preparation
• Drink water to ensure adequate hydration prior to administration of ^18F-FES
• Continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure.

Dosage and administration
• Activity recommended is 222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi)
• Administration: single IV injection of 10 mL or less over 1 to 2 minutes
• Use aseptic technique and radiation shielding when withdrawing and administering FES
• Visually inspect the radiopharmaceutical solution
• FES may be diluted with 0.9% Sodium Chloride Injection, USP
• Assay the dose in a suitable dose calibrator prior to administration

Post administration
• Follow FES injection with an IV flush of 0.9% Sodium Chloride injection, USP

SAFETY OF ^18F-FES
Safety was determined from 1,207 patients with breast cancer receiving at least one Fluoroestradiol F18 administration
Age range = 21-91 years
• 98% were women
  • 76% were post-menopausal

Safety profile was based on clinical studies + NCI investigator’s brochure:
• No serious adverse events
• Adverse events with <1% frequency
  • Injection site pain
  • Dysgeusia
Findings

As seen in Figure 1, the initial $^{18}$F FDG images indicate fluid density along the left breast prosthesis secondary to implant rupture. The images show mild $^{18}$F FDG-avid left axillary and subpectoral nodes, which may be related to metastatic disease or a reaction due to the implant rupture. Stable diffuse activity throughout the axial skeleton and sclerotic osseous lesions without $^{18}$F FDG-avidity above the remainder of the marrow is also observed.

The $^{18}$F FES PET/CT images were acquired with a comparative protocol 2 weeks after the initial $^{18}$F FDG PET/CT and show increased heterogeneous activity throughout the axial and appendicular skeleton with focal areas of increased activity. The left axillary and subpectoral nodes are not indicative of $^{18}$F FES-avidity (Figure 2).

Upon review, the extent of ER-positive osseous metastases is better demonstrated with $^{18}$F FES PET compared to $^{18}$F FDG PET. $^{18}$F FES PET demonstrates increased heterogeneous activity throughout the osseous structures with focal areas of increased activity in comparison to the $^{18}$F FDG PET, which demonstrates increased diffuse activity in the marrow without focal $^{18}$F FDG-avid lesions (Figure 3).
Discussion

In this particular case, the utilization of $^{18}$F FES PET/CT helped confirm that the $^{18}$F FDG-avid left axillary and sub-pectoral lymph nodes were not due to ER-positive metastatic disease but possibly related to implant rupture. Additionally, the $^{18}$F FES PET better demonstrated metastatic osseous lesions with low $^{18}$F FDG-avidity.

Ultimately, the $^{18}$F FDG PET/CT helped confirm that there was no active metastatic process while the concurrent $^{18}$F FES PET/CT helped reinforce the extent of ER density in the metastatic lesions throughout the body in a patient under active treatment with AI and CDK4/6 inhibitors. Since disease progression was not observed on either the $^{18}$F FES PET/CT or the $^{18}$F FDG PET/CT, there was no change in the patient’s treatment management.

Examination protocol

Scanner: Biograph mCT Flow
Imaging software: syngo®.via

<table>
<thead>
<tr>
<th>$^{18}$F FDG PET</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injected dose</td>
<td>10.7 mCi (396 MBq)</td>
</tr>
<tr>
<td>Post-injection delay</td>
<td>60 min</td>
</tr>
<tr>
<td>Acquisition</td>
<td>1.0 mm/s 200 x 200 matrix</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$^{18}$F FES PET</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injected dose</td>
<td>5.5 mCi (202 MBq)</td>
</tr>
<tr>
<td>Post-injection delay</td>
<td>80 min</td>
</tr>
<tr>
<td>Acquisition</td>
<td>1.0 mm/s 200 x 200 matrix</td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The outcomes achieved by the Siemens Healthineers customer described herein were achieved in the customer’s unique setting. Since there is no “typical” hospital and many variables exist (eg, hospital size, case mix, level of IT adoption) there can be no guarantee that others will achieve the same results.

Conclusion

$^{18}$F FES PET/CT—in conjunction with $^{18}$F FDG PET/CT—is a robust imaging radiotracer in the evaluation of ER-positive breast cancer when $^{18}$F FDG PET/CT is inconclusive. In addition, $^{18}$F FES PET is valuable in evaluating lesions with low $^{18}$F FDG-avidity, which is most commonly seen in patients with recurrent metastatic invasive lobular breast cancer.
The dosimetry data show that there are slight variations in abdominal and pelvic areas (3). The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.

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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Newborn (3.4 kg)</th>
<th>1-year old (9.8 kg)</th>
<th>5-year old (19 kg)</th>
<th>10-year old (32 kg)</th>
<th>15-year old (57 kg)</th>
<th>Adult (70 kg)</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>0.18</td>
<td>0.19</td>
<td>0.11</td>
<td>0.058</td>
<td>0.053</td>
</tr>
<tr>
<td>Ureter</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>Stomach 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>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>Muscle</td>
<td>0.58</td>
<td>0.26</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>0.068</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.
* The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.
* LLI = lower large intestine; ** ULI = upper large intestine

The recommended dose is 0.5 to 10 mCi (185 to 370 MBq) 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.
- Upon completion of the PET study, request the patient to fast for at least one hour.
- Screen 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, instruct the patient to fast for 4 to 6 hours prior to the drug's injection.
- In the cardiology setting, the administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F 18 Injection facilitates localization of cardiac ischemia.
- Within the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to Fludeoxyglucose F 18 injection.
- Within 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.
- A lactating woman should pump and discard breastmilk for 9 hours after administration of Fludeoxyglucose F 18 Injection (8.8).
- Note: the administration of glucose prior to (and during) Fludeoxyglucose F 18 Injection may affect the accuracy of procedure.
Fludeoxyglucose F 18 has the molecular formula of \( \text{FDG} \) and has the following chemical structure:

![Chemical Structure of FDG](image)

### 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.
- 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 vials containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL).
- Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/v 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 postmarketing setting. Have emergency resuscitation equipment and personnel immediately available.

### 7 DRUG INTERACTIONS

The 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

**Risk Summary**

Data from published case series and case reports describe Fludeoxyglucose F 18 Injection crossing the placenta with uptake by the fetus (see Data). All radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. However, published studies that describe Fludeoxyglucose F 18 Injection use in pregnant women have not identified a risk of drug-associated major birth defects, miscarriage, or adverse maternal or fetal outcomes. If considering Fludeoxyglucose F 18 Injection administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from the Fludeoxyglucose F 18 Injection and the gestational timing of exposure. The estimated background risk for major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

**Data**

Human Data

Data from published case series and case reports describe Fludeoxyglucose F 18 Injection crossing the placental barrier and utilization of radioactivity throughout the body of the fetus. The estimated fetal absorbed radiation dose from the maximum labeled dose (370 MBq) of Fludeoxyglucose F 18 was 10 mGy with first trimester exposure to PET alone and 20 mGy with first trimester exposure to PET/CT scan combination. Long-term adverse radiation effects to a child exposed to Fludeoxyglucose F 18 Injection in utero are unknown. No adverse fetal effects or radiation-related risks have been identified for diagnostic procedures involving less than 50 mGy, which represents less than 20 mGy fetal doses.

#### 8.2 Lactation

**Risk Summary**

A published case report and case series show the presence of Fludeoxyglucose F 18 Injection in human milk following administration. There are no data on the effects of Fludeoxyglucose F 18 Injection on the breastfed infant or the effects on milk production. Exposure of Fludeoxyglucose F 18 Injection to a breastfed infant can be minimized by temporary discontinuation of breastfeeding (see Clinical Considerations). The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Fludeoxyglucose F 18 Injection, any potential adverse effects to the breastfed child from Fludeoxyglucose F 18 Injection or from the underlying maternal condition.

### 11 DESCRIPTION

#### 11.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[\(^{18}\text{F}\)]fluoro-D-glucose has the molecular formula of \( \text{C}_{12}\text{H}_{16}\text{FO}_{6} \) with a molecular weight of 181.26, and has the following chemical structure:

![Chemical Structure of FDG](image)

### Clinical Considerations

To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breast milk and avoid close (breast) contact with the infant for at least 9 hours after the administration of Fludeoxyglucose F 18 Injection.

### 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 and radiology settings, the safety and effectiveness of Fludeoxyglucose F 18 Injection have not been established in pediatric patients.

### 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 \([\text{F}^{18}]\text{FDG}\)-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. F 18 is used to assess glucose metabolism.

### Table 2. Principal Radiation Emission Data for Fluorine F 18

<table>
<thead>
<tr>
<th>Radiation/Emission</th>
<th>% Per Disintegration</th>
<th>Mean Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron ((\beta^+))</td>
<td>96.73</td>
<td>249.8 keV</td>
</tr>
<tr>
<td>Gamma ((\gamma))</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-11026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 Rh/mCi (1.35 x 10^(-2) Gyh/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 intersection 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 calibration are shown in Table 4.

### Table 4. Physical Decay Chart for Fluorine F 18

<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
In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fluodeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fluodeoxyglucose 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 Fluodeoxyglucose 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 in rate of phosphorylation activity, (3) a reduction of phosphate activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fluodeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fluodeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fluodeoxyglucose 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 converted into glucose. 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 myocardium is metabolized immediately instead of being converted into glucose. Under these conditions, phosphorylated Fluodeoxyglucose 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.

12.3 Pharmacokinetics

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

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

Metabolism: Fluodeoxyglucose F 18 is transported into cells and phosphorylated to [F]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[F]FDM-6-phosphate) (feedback-inhibited). Metabolism of [F]-FDG-6-phosphate to 2-deoxy-2-[F]fluoro-6-phospho-D-mannose ([F]-FDM-6-phosphate) occurs in normal tissues and is minimal in tumors. While the predominant metabolite of [F]-FDG is [F]-FDG-6-phosphate, it is not the only metabolite. Other glucoses and fluorinated compounds (e.g., 2-deoxy-2 chloro-6-phospho-D-glucose (ClDG-6-phosphate), 2-deoxy-2-chloro-6 phospho-D-mannose (ClDG)) have been identified. Biodistribution and metabolism of ClDG are presumed to be similar to Metabolism: Fluodeoxyglucose F 18 is transported into cells and phosphorylated to [F]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[F]fluoro-6-phospho-D-mannose ([F]-FDM-6-phosphate). Metabolism of [F]-FDG-6-phosphate to 2-deoxy-2-[F]fluoro-6-phospho-D-mannose ([F]-FDM-6-phosphate) occurs in normal tissues and is minimal in tumors. While the predominant metabolite of [F]-FDG is [F]-FDG-6-phosphate, it is not the only metabolite. Other glucoses and fluorinated compounds (e.g., 2-deoxy-2 chloro-6-phospho-D-glucose (ClDG-6-phosphate), 2-deoxy-2-chloro-6 phospho-D-mannose (ClDG)) have been identified. Biodistribution and metabolism of ClDG are presumed to be similar to Fluodeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (ClDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDG). Fluodeoxyglucose F 18 injection PET imaging confirmed previously identified on-ical EGs and spheroidal EGs. 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 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.

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, liver, bone, and pancreatic lesions. All these studies had at least 50 patients and used pathologic 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 diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained.

PET/CT Case Study

PETNET Solutions
CERIANNA™ (fluoroestradiol F 18) Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CERIANNA™ safely and effectively. See full prescribing information for CERIANNA.

CERIANNA™ (fluoroestradiol F 18) Injection, for intravenous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE
CERIANNA is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) imaging for the detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.

Limitations of Use
Tissue biopsy should be used to confirm recurrence of breast cancer and to verify ER status by pathology. CERIANNA is not useful for imaging other receptors, such as human epidermal growth factor receptor 2 (HER2) and the progesterone receptor (PR).

DOSEAGE AND ADMINISTRATION
Recommended dose is 222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi), administered as an intravenous injection over 1 to 2 minutes. (2.2)

Recommended imaging start time is 80 minutes after the intravenous administration of CERIANNA. The radiation effective dose resulting from administering CERIANNA scan. (5.1)

Recommended imaging start time is 80 minutes after the intravenous administration of CERIANNA. (8.2)

Dosage and Administration Instructions
• Follow the CERIANNA injection with an intravenous flush of 0.9% Sodium Chloride injection, USP.

ADVERSE REACTIONS
Reported adverse reactions include: injection-site pain and dysgeusa

USE IN SPECIFIC POPULATIONS
• Lactation: Interrupt breastfeeding. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration. (8.2)

PATIENT COUNSELING INFORMATION
Revised: 07/2020

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FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USAGE
CERIANNA is indicated for use in postmenopausal women with recurrent or metastatic breast cancer.

2 DOSAGE AND ADMINISTRATION
2.1 Radiation Safety - Drug Handling
CERIANNA is a radioactive drug. Only authorized persons qualified by training and experience should receive, use, and administer CERIANNA. Handle CERIANNA with appropriate safety measures to minimize radiation exposure during administration. [See Warnings and Precautions (5.2).] Use waterproof gloves and effective radiation shielding, including syringe shields, when preparing and handling CERIANNA.

2.2 Recommended Dosage and Administration Instructions
Recommended Dosage
The recommended amount of radioactivity to be administered for PET imaging is 222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi), administered as a single intravenous injection of 10 mL or less over 1 to 2 minutes.

Preparation and Administration
• For patient preparation instructions, see (2.3).
• Use aseptic technique and radiation shielding when withdrawing and administering CERIANNA.
• Visually inspect the radiopharmaceutical solution. Do not use it if it contains particulate matter or if it is cloudy or discolored (CERIANNA is a clear, colorless solution).
• CERIANNA may be diluted with 0.9% Sodium Chloride Injection, USP.

2.3 Patient Preparation
Assessment for Drug Interactions
Image patients with CERIANNA prior to starting systemic endocrine therapies that target ER (e.g., ER modulators and ER down-regulators) [See Drug Interactions (7.1)].

Patient Hydration and Voiding
Instruct patients to drink water to ensure adequate hydration prior to administration of CERIANNA and to continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure.

Pregnancy Status
Assessment of pregnancy status is recommended in females of reproductive potential before administering CERIANNA.

2.4 Image Acquisition
Position the patient supine with arms above the head, if possible. The recommended start time for image acquisition is 80 minutes after the intravenous administration of CERIANNA. Scan duration adapted from the range of 20 minutes to 30 minutes and imaging start times adapted within the range of 20 minutes to 80 minutes may be customized according to the equipment used and patient and tumor characteristics for optimal image quality.

2.5 Image Interpretation
Update of Fluorodestriol F 18 depends on ER density and function in tumors and physiologic tissue, including in liver, ovary, and uterus. Detection of ER-positive tumors should be based on comparison with tissue background outside of organs with high physiologic uptake and regions with high activity due to hepatobiliary and urinary excretion.

2.6 Radiation Dosimetry
Radiation absorbed dose estimates are shown in Table 1 for organs and tissues of adults from intravenous administration of CERIANNA to an adult weighing 70 kg is estimated to be 4.9 mSv. Critical organs include the liver, gallbladder, and uterus. When PET/CT is performed, exposure to radiation will increase by an amount dependent on the settings used for the CT acquisition.

Table 1. Estimated Radiation Absorbed Doses in Various Organs/Tissues in Adults Who Received FLUORODESTRIOL F 18

<table>
<thead>
<tr>
<th>Organ</th>
<th>Mean Absorbed Dose Per Unit of Activity Administered (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.023</td>
</tr>
<tr>
<td>Brain</td>
<td>0.01</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.009</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>0.102</td>
</tr>
<tr>
<td>Lower large intestine</td>
<td>0.012</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.027</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.014</td>
</tr>
<tr>
<td>Upper large intestine</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart wall</td>
<td>0.026</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.035</td>
</tr>
<tr>
<td>Liver</td>
<td>0.126</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.017</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.021</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.018</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.023</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.013</td>
</tr>
<tr>
<td>Bone surface</td>
<td>0.014</td>
</tr>
<tr>
<td>Skin</td>
<td>0.005</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.015</td>
</tr>
<tr>
<td>Testes</td>
<td>0.012</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.014</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>0.012</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.039</td>
</tr>
<tr>
<td>Lens</td>
<td>0.009</td>
</tr>
<tr>
<td>Effective dose</td>
<td>0.022 mSv/MBq</td>
</tr>
</tbody>
</table>
CERIANNA contains fluoroestradiol fluorine 18 (F 18), a synthetic estrogen analog. CERIANNA is sterile, clear, colorless solution for intravenous injection, with an osmolality of 340 mOsM. Its pH ranges between 4.5 to 7.0. The composition of the final product in 40 mL solution is fluoroestradiol no more than 5 μg, fluoroestradiol F 18 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL), sodium ascorbate 0.44% w/v in sodium chloride 0.9% w/v, and ethanol no more than 3.2% w/v.

11.2 Physical Characteristics
CERIANNA is radiolabeled with F 18, a cyclotron produced radionuclide that decays by positron emission to stable oxygen 18 with a half-life of 109.8 minutes. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 2).

### Table 2. Principal Radiation Produced From Decay of Fluorine 18 Radiation

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Energy Level (keV)</th>
<th>% Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positron</td>
<td>249.8</td>
<td>96.9</td>
</tr>
<tr>
<td>Gamma</td>
<td>511</td>
<td>193.5</td>
</tr>
</tbody>
</table>

11.3 External Radiation
The point source air-kerma coefficient for F 18 is 3.75 x 10^15 Gy m^2 (Bq s). The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by F 18 that results from various thicknesses of lead shielding is shown in Table 3. The use of cm Pb decreases the radiation transmission (i.e., exposure) by a factor of about 10,000.

### Table 3. Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

<table>
<thead>
<tr>
<th>Shield Thickness cm of Lead (Pb)</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>0.01</td>
</tr>
<tr>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>8</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Fluoroestradiol F 18 binds ER. The following binding affinity: KD = 0.13 ± 0.02 nM, Bmax = 1901 ± 89 fmol/mg, and IC50 = 0.085 nM, was determined in an ER-positive human breast cancer cell line (MCF-7).

12.2 Pharmacodynamics
The relationship between fluoroestradiol F 18 plasma concentrations and image interpretation has not been studied. Fluoroestradiol F 18 uptake measured by PET in human tumors is directly proportional to tumor ER expression measured by in vitro assays.

12.3 Pharmacokinetics

Distribution
After intravenous injection, 95% of fluoroestradiol F 18 is bound to plasma proteins. Fluoroestradiol F 18 distributes primarily to hepatobiliary system, and also to small and large intestines, heart wall, blood, kidney, uterus and bladder.

Metabolism
Fluoroestradiol F 18 is metabolized in the liver. At 20 minutes after injection, approximately 20% of circulating radioactivity in the plasma is in the form of non-metabolized fluoroestradiol F 18. At 2 hours after injection, circulating fluoroestradiol F 18 levels are less than 5% of peak concentration.

Excretion
Elimination is by biliary and urinary excretion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
No long-term studies in animals were performed to evaluate the carcinogenic potential of CERIANNA.

Mutagenesis
Fluoroestradiol was evaluated by in vitro bacterial reverse mutation assay (Ames test) and in vitro L5178Y/Tk+/+ mouse lymphoma mutagenesis assay. Fluoroestradiol was not negative for genotoxicity by Ames test at up to 1.25 μg per plate for 5 tester strains (Salmonella typhimurium tester strains TA98, TA100, TA1535 and TA1537 and Escherichia Coli tester strain WP2 uvrA) in the presence or absence of S9 metabolic activation. Fluoroestradiol was negative for genotoxicity by L5178Y/Tk+/+ mouse lymphoma mutagenesis assay up to 8 ng/ml, in the presence or absence of S9 metabolic activation. Potential in vivo genotoxicity of fluoroestradiol was evaluated in a rat micronucleus assay. In this assay, fluoroestradiol did not increase the number of micronucleated polychromatic erythrocytes (MN-PCs) at 50 μg/kg/day, when given for 14 consecutive days. However, CERIANNA has the potential to be mutagenic because of the F 18 isotope.

Impairment of Fertility
No studies in animals have been performed to evaluate potential impairment of fertility in males or females.
The effectiveness of CERIANNA for detecting ER-positive non-primary breast cancer lesions was evaluated based on published study reports of fluoroestradiol F 18. Study 1 (NCT01986569) enrolled 90 women (median age 55 years, 39% premenopausal) with histologically confirmed invasive breast cancer. The patients had first known or suspected recurrence of treated breast cancer or stage IV metastatic breast cancer. Recent biopsy of lesions outside of bone and areas with high physiologic fluoroestradiol F 18 uptake was also required [see Dosage and Administration (2.5)]. Patients concurrently using estrogen receptor modulators or fulvestrant discontinued them 60 days prior to fluoroestradiol F 18 administration. Concurrent use of aromatase inhibitors was permitted. Three image readers were blinded to all clinical information, except for the location of the largest biopsied lesion, for which pathologists independently provided an Allred score (0 to 8). The image readers scored the intensity of FES uptake on a three-point scale relative to normal biodistribution as either “decreased,” “equivocal,” or “increased” (1 to 3).

Image reader performance for distinguishing between ER-positive and ER-negative fluoroestradiol F 18 uptake was compared to biopsy in 85 patients. Of the 47 patients with positive biopsy (Allred score ≥ 3), 36 were positive on imaging (majority reader score = 3). Ten of 11 patients with false negative imaging had Allred scores between 3 and 6 [see Warnings and Precautions (5.1)]. Of the 38 patients with negative biopsy, all 38 were negative on imaging.

Study 2 (NCT00602043) in 13 patients showed similar results.

HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
CERIANNA is supplied in a 50 mL multiple-dose glass vial (NDC# 72874-001-01) containing a clear, colorless injection solution at a strength of 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) fluoroestradiol F 18 at the end of synthesis. Each vial contains multiple doses and is enclosed in a shield container to minimize external radiation exposure.

16.2 Storage and Handling
Storage
Store CERIANNA at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Store CERIANNA upright in the original container with radiation shielding. The expiration date and time are provided on the container label. Use CERIANNA within 10 hours from the time of the end of synthesis.

Handling
This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

PATIENT COUNSELING INFORMATION

Radiation Risks
Advise patients of the radiation risks of CERIANNA [see Warnings and Precautions (5.2)]. Instruct patients to drink water to ensure adequate hydration prior to administration of CERIANNA and to continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure [see Dosage and Administration (2.3)].

Pregnancy
Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with CERIANNA [see Use in Specific Populations (8.1)].

Lactation
Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration in order to minimize radiation exposure to a breastfed infant [see Use in Specific Populations (8.2)].
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