

# **$^{18}\text{F}$ -FES PET/CT distinction of ER-positive lesions in a patient with metastatic breast cancer**

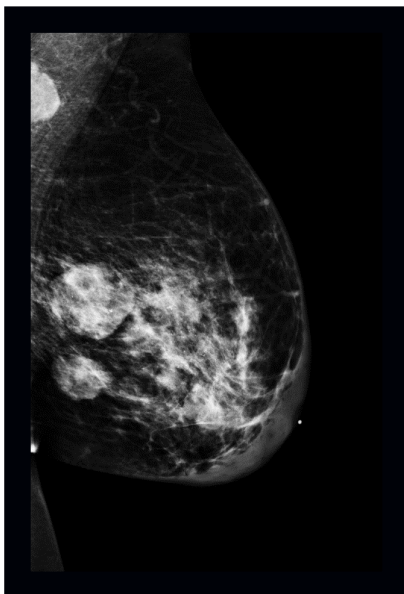
By Misty Long, ARRT, RT (R)(N), Siemens Healthineers Molecular Imaging, Knoxville, Tennessee, USA and Steve Wozniak, BS, CNMT, PET, 210 PET Imaging, Cary, North Carolina, USA  
Data and images courtesy of 210 PET Imaging, Cary, North Carolina, USA

## **History**

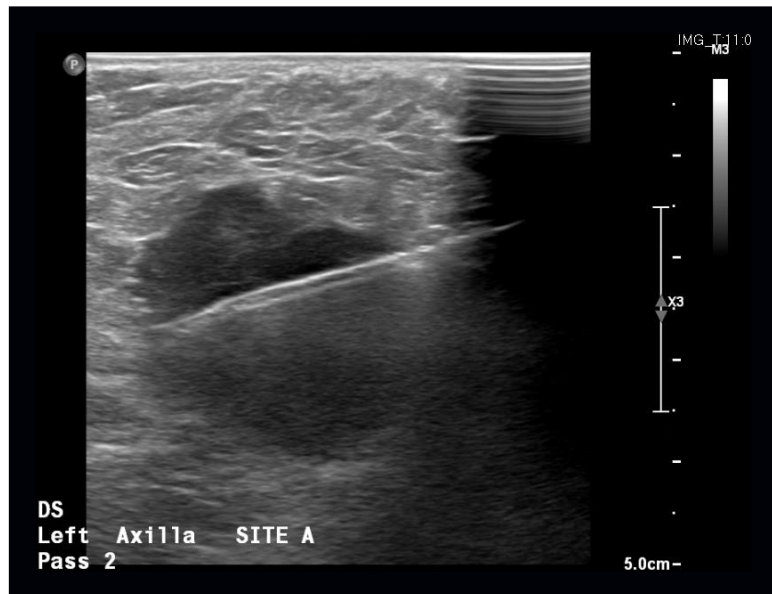
An approximately 65-year-old female underwent routine mammography in which suspicious masses were detected at the 3-o'clock position of the left breast. Widespread suspicious calcifications were noted with

a recommendation to biopsy for possible metastatic disease (Figure 1). Ultrasound-guided, left breast biopsy performed based on suspicious findings of the mammogram as well as the left

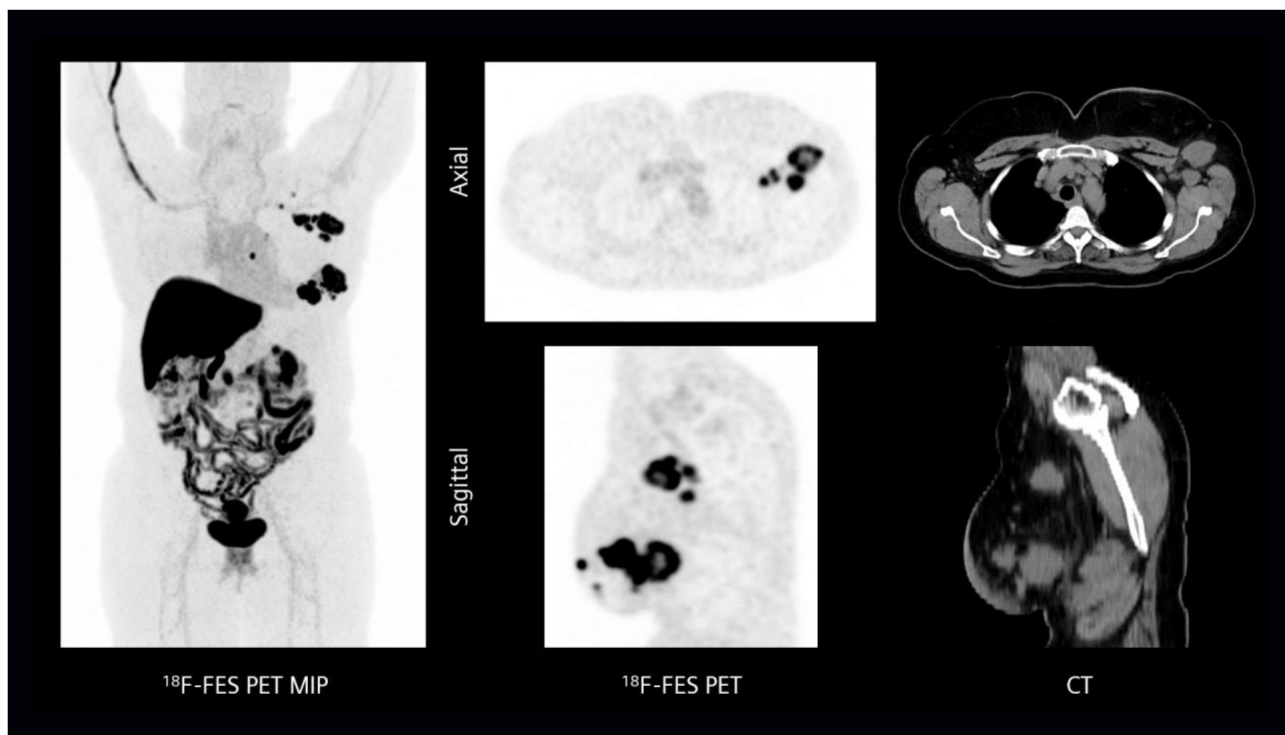
axillary lymph node revealed left inflammatory breast cancer, which was identified as a grade 3 invasive ductal carcinoma (Figure 2).  $^{18}\text{F}$ -FES PET/CT was ordered due to suspicion of metastatic disease.



**1** Routine mammography shows widespread suspicious masses at the 3-o'clock position of the left breast.



**2** Ultrasound-guided, left breast biopsy performed based on suspicious findings of the mammogram.



**3**  $^{18}\text{F}$ -FES PET MIP and axial and sagittal PET and CT views reveal multifocal ER-positive lesions within the left breast, multiple enlarged left axillary lymph nodes, and a solitary enlarged left internal mammary lymph node.

## Findings

Approximately 1 hour following 6.2 mCi (229 MBq) intravenous (IV) administration of Cerianna™ (Fluoroestradiol F18) injection<sup>[a,b]</sup> a PET imaging agent for use in recurrent or metastatic ER-positive breast cancer as an adjunct to biopsy—the patient was scanned on Biograph Vision™ PET/CT. A PET study using a step-and-shoot method acquisition protocol was performed after an initial CT for attenuation correction. PET images were acquired from the skull vertex to the mid-

thigh and were acquired at 9 bed positions at 3 minutes per bed, resulting in a 27-minute total scan time, and then reconstructed with a 440 x 440 matrix.

As seen in Figure 3,  $^{18}\text{F}$ -FES PET images reveal multifocal estrogen-receptor (ER)-positive lesions within the left breast, multiple enlarged left axillary lymph nodes, and a solitary enlarged left internal mammary lymph node. Based on the  $^{18}\text{F}$  FES PET/CT findings, the patient

underwent anti-androgen therapy, along with chemotherapy agents, which included cyclophosphamide and doxorubicin. The patient was switched from doxorubicin to paclitaxel after approximately 1 month.

A 4-month follow-up  $^{18}\text{F}$ -FDG PET/CT scan was ordered for subsequent treatment strategy (STS) decision to assess therapy response and detect the presence of residual disease.

<sup>[a]</sup> Please see Indications and Important Safety Information for CERIANNA (Fluoroestradiol F 18 [ $^{18}\text{F}$ -FES]) Injection on page 3-4. For full Prescribing Information, please see pages 8-15.

<sup>[b]</sup> Cerianna™ is a trademark owned or licensed by GE HealthCare Technologies Inc., its subsidiaries, and/or affiliates.

## CERIANNA™ (fluoroestradiol F 18) Injection

### INDICATIONS AND USAGE

CERIANNA is 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).

### IMPORTANT SAFETY INFORMATION

#### Contraindications

None.

#### Warnings and Precautions

##### Risk of misdiagnosis

- **Inadequate tumor characterization and other ER-positive pathology:** Breast cancer may be heterogeneous within patients and across time. CERIANNA images ER and is not useful for imaging other receptors such as HER2 and PR. The uptake of fluoroestradiol F 18 is not specific for breast cancer and may occur in a variety of ER-positive tumors that arise outside of the breast, including from the uterus and ovaries. Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer.
- **False negative CERIANNA scan:** A negative CERIANNA scan does not rule out ER-positive breast cancer. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative CERIANNA scan.

##### Radiation risks

Diagnostic radiopharmaceuticals, including CERIANNA, expose patients to radiation. Radiation exposure is associated with dose- dependent increased risk of cancer. Ensure safe drug handling and patient preparation procedures (including adequate hydration and voiding) to protect patients and health care providers from unintentional radiation exposure.

##### Pregnancy status

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

#### Adverse Reactions

In clinical trials (n=1207) the most common adverse reactions seen occurred at a rate < 1%: were injection-site pain and dysgeusia.

#### Use in Specific Populations

##### Pregnancy risk summary

All radiopharmaceuticals, including CERIANNA, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of radiation dose. Advise a pregnant woman of the potential risks of fetal exposure to radiation from administration of CERIANNA.

There are no available data on CERIANNA use in pregnant women. No animal reproduction studies using fluoroestradiol F 18 have been conducted to evaluate its effect on female reproduction and embryo-fetal development.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

##### Lactation risk summary

There are no data on the presence of fluoroestradiol F 18 in human milk, or its effects on the breastfed infant or milk production. Lactation studies have not been conducted in animals. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration in order to minimize radiation exposure to a breastfed infant.

##### Pediatric use

The safety and effectiveness of CERIANNA in pediatric patients have not been established.

##### Geriatric use

Clinical studies of fluoroestradiol F 18 injection did not reveal any difference in pharmacokinetics or biodistribution in patients aged 65 and over.

(continued)

## **CERIANNA™ (fluoroestradiol F 18) Injection (cont.)**

### **Drug Interactions**

#### **Systemic endocrine therapies that target estrogen receptors**

Certain classes of systemic endocrine therapies, including ER modulators and ER down-regulators, block ER, reduce the uptake of fluoroestradiol F 18, and may reduce detection of ER-positive lesions after administration of CERIANNA. Drugs from these classes such as tamoxifen and fulvestrant may block ER for up to 8 and 28 weeks, respectively. Do not delay indicated therapy in order to administer CERIANNA. Administer CERIANNA prior to starting systemic endocrine therapies that block ER.

**To report SUSPECTED ADVERSE REACTIONS, contact GE HealthCare at 800 654 0118 (option 2, then option 1) or by email at [GPV.drugsafety@ge.com](mailto:GPV.drugsafety@ge.com) or the FDA at 800 FDA 1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### **DOSAGE FORMS 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**

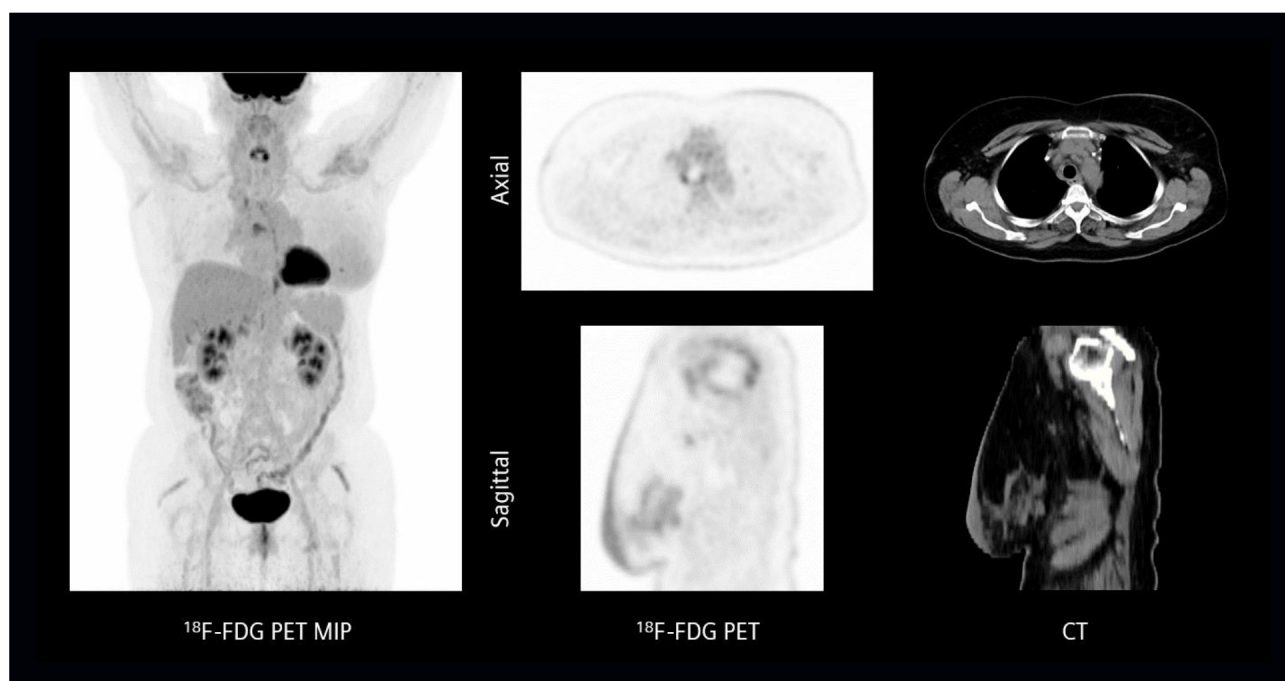
- Drink water to ensure adequate hydration prior to administration of <sup>18</sup>F-FES
- Continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure

#### **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



**4**  $^{18}\text{F}$ -FDG PET MIP and axial and sagittal PET and CT views at the 4-month follow-up show near-normal  $^{18}\text{F}$ -FDG uptake in the area of the previously detected breast and nodal lesions along with decreased soft-tissue nodularity of the left breast, marked interval decrease in size of left axillary/retropectoral lymphadenopathy, and interval resolution of a mildly enlarged left internal mammary chain lymph node.

At the 4-month follow-up scan, the patient received 10.2 mCi (377 MBq) IV administration of Fludeoxyglucose F 18 ( $^{18}\text{F}$ -FDG) Injection<sup>[4]</sup> approximately 47 minutes prior to undergoing PET/CT on Biograph Vision. A skull base to mid-thigh (SBMT) PET study using a step-and-shoot method acquisition protocol was performed after an initial CT for attenuation correction. The SBMT PET study was acquired at 7 bed positions at 2 minutes per bed, resulting in a 14-minute total scan

time, and then reconstructed with a 440 x 440 matrix.  $^{18}\text{F}$ -FDG PET images shown in Figure 4 show near-normal  $^{18}\text{F}$ -FDG uptake in the area of the previously detected breast and nodal lesions along with decreased soft-tissue nodularity of the left breast, marked interval decrease in size of left axillary/retropectoral lymphadenopathy, and interval resolution of a mildly enlarged left internal mammary chain lymph node.

The absence of significant hypermetabolism and gross reduction in lesion size as shown by follow-up  $^{18}\text{F}$ -FDG PET/CT study suggests a positive response to antiandrogen and adjunct therapies, which were administered based on identification of ER-positive lesions by  $^{18}\text{F}$ -FES PET/CT.

<sup>[4]</sup> Please see Indications and Important Safety Information for Fludeoxyglucose F 18 ( $^{18}\text{F}$ -FDG) Injection on page 6. For full Prescribing Information, please see pages 16-18.

## Fludeoxyglucose F 18 injection

### INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection ( $^{18}\text{F}$ -FDG) 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 Risk:** 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 ensure 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.
- **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.

### 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) 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.

- **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.

Fludeoxyglucose F 18 Injection is manufactured and distributed by PETNET Solutions, Inc., 810 Innovation Drive, Knoxville, TN 37932

## Discussion

According to the American Cancer Society, breast cancer is the second-leading cause of cancer death in women after lung cancer and is the most common cancer diagnosed among women in the US, excluding skin cancers. Over 75% of primary breast cancers are hormone-receptor positive. DeSantis et al indicates that the incidence rates of hormone-receptor positive breast cancer are on the rise in the US. This may be due to the increasing prevalence of excess body weight as well as declining fertility rates.<sup>1</sup>

The utility of PET/CT-directed management of ER-positive primary tumors is essential as patients with distant metastatic disease are rarely cured but often live with disease for years. Therefore, more targeted approaches for early detection strategies are needed in long-term survival care planning.

## Conclusion

Endocrine therapies allow a more favorable response in the treatment of patients with distant metastatic breast cancer from an ER-positive primary tumor with fewer side effects. Therefore, <sup>18</sup>F-FES PET/CT could prove advantageous in non-invasively assessing ER+ disease, assisting clinicians in making informed treatment decisions, and could be cost-effective for patients considering combinations of endocrine therapy and other targeted agents.<sup>2</sup>

## Examination protocol

Scanner: Biograph Vision 450

### <sup>18</sup>F-FES PET

Injected dose	6.2 mCi (229 MBq) <sup>18</sup> F-FES
Post-injection delay	60 minutes
Acquisition	9 bed positions/3 minutes per bed
Image reconstruction	440 x 440 matrix

### CT

Tube voltage	120 kV
Tube current	11 ref mAs
Slice collimation	1.2 mm
Slice thickness	5.0 mm

### <sup>18</sup>F-FDG PET

Injected dose	10.2 mCi (377 MBq) <sup>18</sup> F-FDG
Post-injection delay	47 minutes
Acquisition	7 bed positions/2 minutes per bed
Image reconstruction	440 x 440 matrix

### CT

Tube voltage	120 kV
Tube current	85 ref mAs
Slice collimation	1.2 mm
Slice thickness	5.0 mm

The outcomes achieved by the Siemens Healthineers customers 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.

## References

- <sup>1</sup> DeSantis CE, Ma J, Gaudet MM et al. Breast cancer statistics, 2019. *CA Cancer J Clin.* 2019;69:438-451. doi:10.3322/caac.21583.
- <sup>2</sup> Liao GJ, Clark AS, Schubert EK, Mankoff DA. <sup>18</sup>F-Fluoroestradiol PET: Current Status and Potential Future Clinical Applications. *J Nucl Med.* 2016;57(8):1269-75. doi:10.2967/jnumed.116.175596.



**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. (1)

**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). (1, 5.1)

**DOSAGE 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 (range 20 minutes to 80 minutes) after drug administration. (2.4)
- See full prescribing information for additional preparation, administration, imaging, and radiation dosimetry information. (2)

**DOSAGE FORMS AND STRENGTHS**

Injection: 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of fluoroestradiol F 18 in a multiple-dose vial. (3)

**CONTRAINDICATIONS**

- None. (4)

**WARNINGS AND PRECAUTIONS**

- Risk of Misdiagnosis.** Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative CERIANNA scan. (5.1)
- Radiation Risks.** Ensure safe drug handling and patient preparation procedures to protect patients and health care providers from unintentional radiation exposure. (2.1, 2.3, 5.2)

**ADVERSE REACTIONS**

Reported adverse reactions include: injection-site pain and dysgeusia (6)

To report SUSPECTED ADVERSE REACTIONS, contact GE HealthCare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- Drugs such as tamoxifen and fulvestrant that block the estrogen receptor reduce the uptake of fluoroestradiol F 18. Do not delay indicated therapy in order to administer CERIANNA. Image patients with CERIANNA prior to starting systemic endocrine therapies that block ER. (2.3, 7.1)

**USE IN SPECIFIC POPULATIONS**

- Lactation: Interrupt breastfeeding. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2023

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\* Sections or subsections omitted from the full prescribing information are not listed.



## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

CERIANNA is 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).

### 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 Dosage and Administration 2.3.
- Use aseptic technique and radiation shielding when withdrawing and administering CERIANNA.
- Visually inspect the radiopharmaceutical solution. Do not use 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.
- Assay the dose in a suitable dose calibrator prior to administration.

##### Post-Administration Instructions

- Follow the CERIANNA injection with an intravenous flush of 0.9% Sodium Chloride injection, USP.
- Dispose of any unused CERIANNA in compliance with applicable regulations.

#### 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

Uptake of fluoroestradiol 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. The radiation effective dose resulting from administration of 222 MBq (6 mCi) 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 FLUOROESTRADIOL F 18**

Organ	Mean Absorbed Dose Per Unit of Activity Administered (mGy/MBq)
Adrenals	0.023
Brain	0.01
Breasts	0.009
Gallbladder	0.102
Lower large intestine	0.012
Small intestine	0.027
Stomach	0.014
Upper large intestine	0.03
Heart wall	0.026
Kidney	0.035
Liver	0.126
Lungs	0.017
Muscle	0.021
Ovaries	0.018
Pancreas	0.023
Red Marrow	0.013
Bone surface	0.014
Skin	0.005
Spleen	0.015
Testes	0.012
Thymus	0.014
Thyroid	0.012
Urinary bladder	0.05
Uterus	0.039
Lens	0.009
Effective dose = 0.022 mSv/MBq	

## 3 DOSAGE FORMS 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 fluoroestradiol F 18 at end of synthesis.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risk of Misdiagnosis

#### Inadequate Tumor Characterization and Other ER-Positive Pathology

Breast cancer may be heterogeneous within patients and across time. CERIANNA images ER and is not useful for imaging other receptors such as HER2 and PR. The uptake of fluoroestradiol F 18 is not specific for breast cancer and may occur in a variety of ER-positive tumors that arise outside of the breast, including from the uterus and ovaries. Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer.

#### False Negative CERIANNA Scan

A negative CERIANNA scan does not rule out ER-positive breast cancer [see *Clinical Studies (14)*]. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative CERIANNA scan.

### 5.2 Radiation Risks

Diagnostic radiopharmaceuticals, including CERIANNA, expose patients to radiation [see *Dosage and Administration (2.6)*]. Radiation exposure is associated with a dose-dependent increased risk of cancer. Ensure safe drug handling and patient preparation procedures to protect patients and health care providers from unintentional radiation exposure [see *Dosage and Administration (2.1)* and *(2.3)*].

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of CERIANNA was evaluated from published clinical studies of 1,207 patients with breast cancer receiving at least one fluoroestradiol F 18 administration. The following adverse reactions occurred at a rate < 1%:

- *General disorders:* injection-site pain
- *Neurological and gastrointestinal disorders:* dysgeusia

## 7 DRUG INTERACTIONS

### 7.1 Systemic Endocrine Therapies that Target Estrogen Receptors

Certain classes of systemic endocrine therapies, including ER modulators and ER down-regulators, block ER, reduce the uptake of fluoroestradiol F 18, and may reduce detection of ER-positive lesions after administration of CERIANNA. Drugs from these classes such as tamoxifen and fulvestrant may block ER for up to 8 and 28 weeks, respectively. Do not delay indicated therapy in order to administer CERIANNA. Administer CERIANNA prior to starting systemic endocrine therapies that block ER [see *Dosage and Administration (2.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

All radiopharmaceuticals, including CERIANNA, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of radiation dose. Advise a pregnant woman of the potential risks of fetal exposure to radiation from administration of CERIANNA.

There are no available data on CERIANNA use in pregnant women. No animal reproduction studies using fluoroestradiol F 18 have been conducted to evaluate its effect on female reproduction and embryo-fetal development.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

## 8.2 Lactation

### Risk Summary

There are no data on the presence of fluoroestradiol F 18 in human milk, or its effects on the breastfed infant or milk production. Lactation studies have not been conducted in animals. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration in order to minimize radiation exposure to a breastfed infant.

## 8.4 Pediatric Use

The safety and effectiveness of CERIANNA in pediatric patients have not been established.

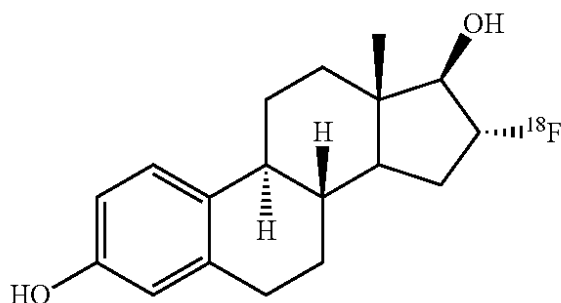
## 8.5 Geriatric Use

Clinical studies of fluoroestradiol F 18 injection did not reveal any difference in pharmacokinetics or biodistribution in patients aged 65 and over.

# 11 DESCRIPTION

## 11.1 Chemical Characteristics

CERIANNA contains fluoroestradiol fluorine 18 (F 18), a synthetic estrogen analog. Chemically, fluoroestradiol F 18 is [18F]16 $\alpha$ -fluoro-3,17 $\beta$ -diol-estratriene-1,3,5(10). The molecular weight is 289.37, and the structural formula is:



CERIANNA is a sterile, clear, colorless solution for intravenous injection, with an osmolarity 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 mcg, 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**

Radiation	Energy Level (keV)	% Abundance
Positron	249.8	96.9
Gamma	511	193.5

### 11.3 External Radiation

The point source air-kerma coefficient for F 18 is  $3.75 \times 10^{-17}$  Gy m<sup>2</sup> / (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 8 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**

Shield Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Fluoroestradiol F 18 binds ER. The following binding affinity:  $K_d = 0.13 \pm 0.02$  nM,  $B_{max} = 1901 \pm 89$  fmol/mg, and  $IC_{50} = 0.085$  nM, was determined in an ER-positive human breast cancer cell line (MCF-7).

### 12.2 Pharmacodynamics

The relationship between fluoroestradiol F18 plasma concentrations and image interpretation has not been studied. Fluoroestradiol F18 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 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 at up to 8 ng/mL in the absence or presence 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-PCEs) at 51 µg/kg/day, when given for 14 consecutive days. However, CERIANNA has the potential to be mutagenic because of the F 18 radioisotope.

#### Impairment of Fertility

No studies in animals have been performed to evaluate potential impairment of fertility in males or females.

## 14 CLINICAL STUDIES

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.

## 16 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 12 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.

## **17 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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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### Fludeoxyglucose F 18 Injection, USP

For intravenous use

Initial U.S. Approval: 2005

#### 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 (1).

#### DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

- In the oncology and neurology settings, instruct patients to fast for 4 to 6 hours prior to the drug's injection. Consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to the drug's administration (5.2).
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection facilitates localization of cardiac ischemia (2.3).

Aseptically withdraw Fludeoxyglucose F 18 Injection from its container and administer by intravenous injection (2).

The recommended dose:

- for adults is 5 to 10 mCi (185 to 370 MBq), in all indicated clinical settings (2.1).
- for pediatric patients is 2.6 mCi in the neurology setting (2.2).

Initiate imaging within 40 minutes following drug injection; acquire static emission images 30 to 100 minutes from time of injection (2).

#### DOSAGE FORMS AND STRENGTHS

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

#### CONTRAINDICATIONS

None.

#### WARNINGS AND PRECAUTIONS

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

#### ADVERSE REACTIONS

Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available (6).

To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### USE IN SPECIFIC POPULATIONS

- Lactation: Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for 9 hours after Fludeoxyglucose F 18 Injection (8.2).
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings (8.4).

#### See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2019

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

### 1.3 Neurology

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

### 2 DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].

#### 2.1 Recommended Dose for Adults

Within the oncology, cardiology and neurology settings, the recommended dose for adults is 5 to 10 mCi (185 to 370 MBq) as an intravenous injection.

#### 2.2 Recommended Dose for Pediatric Patients

Within the neurology setting, the recommended dose for pediatric patients is 2.6 mCi, as an intravenous injection. The optimal dose adjustment on the basis of body size or weight has not been determined [see Use in Special Populations (8.4)].

#### 2.3 Patient Preparation

- To minimize the radiation absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [see Warnings and Precautions (5.2)]. Prior to Fludeoxyglucose F 18 PET imaging in the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug's injection.
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F 18 Injection facilitates localization of cardiac ischemia.

#### 2.4 Radiation Dosimetry

The estimated human absorbed radiation doses (rem/mCi) to a newborn (3.4 kg), 1-year old (9.8 kg), 5-year old (19 kg), 10-year old (32 kg), 15-year old (57 kg), and adult (70 kg) from intravenous administration of Fludeoxyglucose F 18 Injection are shown in Table 1. These estimates were calculated based on human<sup>2</sup> data and using the data published by the International Commission on Radiological Protection<sup>4</sup> for Fludeoxyglucose <sup>18</sup>F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated are the urinary bladder, heart, pancreas, spleen, and lungs.

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

Organ	Newborn (3.4 kg)	1-year old (9.8 kg)	5-year old (19 kg)	10-year old (32 kg)	15-year old (57 kg)	Adult (70 kg)
Bladder wall <sup>b</sup>	4.3	1.7	0.93	0.60	0.40	0.32
Heart wall	2.4	1.2	0.70	0.44	0.29	0.22
Pancreas	2.2	0.68	0.33	0.25	0.13	0.096
Spleen	2.2	0.84	0.46	0.29	0.19	0.14
Lungs	0.96	0.38	0.20	0.13	0.092	0.064
Kidneys	0.81	0.34	0.19	0.13	0.089	0.074
Ovaries	0.80	0.8	0.19	0.11	0.058	0.053
Uterus	0.79	0.35	0.19	0.12	0.076	0.062
LLI wall *	0.69	0.28	0.15	0.097	0.060	0.051
Liver	0.69	0.31	0.17	0.11	0.076	0.058
Gallbladder wall	0.69	0.26	0.14	0.093	0.059	0.049
Small intestine	0.68	0.29	0.15	0.096	0.060	0.047
ULI wall **	0.67	0.27	0.15	0.090	0.057	0.046
Stomach wall	0.65	0.27	0.14	0.089	0.057	0.047
Adrenals	0.65	0.28	0.15	0.095	0.061	0.048
Testes	0.64	0.27	0.14	0.085	0.052	0.041
Red marrow	0.62	0.26	0.14	0.089	0.057	0.047
Thymus	0.61	0.26	0.14	0.086	0.056	0.044
Thyroid	0.61	0.26	0.13	0.080	0.049	0.039
Muscle	0.58	0.25	0.13	0.078	0.049	0.039
Bone surface	0.57	0.24	0.12	0.079	0.052	0.041
Breast	0.54	0.22	0.11	0.068	0.043	0.034
Skin	0.49	0.20	0.10	0.060	0.037	0.030
Brain	0.29	0.13	0.09	0.078	0.072	0.070
Other tissues	0.59	0.25	0.13	0.083	0.052	0.042

<sup>a</sup> MIRDose 2 software was used to calculate the radiation absorbed dose.

<sup>b</sup> The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.

\* LLI = lower large intestine; \*\* ULI = upper large intestine

## 2.5 Radiation Safety – Drug Handling

- Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F 18 Injection to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].
- The dose of Fludeoxyglucose F 18 used in a given patient should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.

## 2.6 Drug Preparation and Administration

- Calculate the necessary volume to administer based on calibration time and dose.
- Aseptically withdraw Fludeoxyglucose F 18 Injection from its container.
- Inspect Fludeoxyglucose F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer the drug if it contains particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

## 2.7 Imaging Guidelines

- Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
- Acquire static emission images 30 to 100 minutes from the time of injection.

## 3 DOSAGE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Radiation Risks

Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.5)].

### 5.2 Blood Glucose Abnormalities

In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

## 6 ADVERSE REACTIONS

Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting. Have emergency resuscitation equipment and personnel immediately available.

## 7 DRUG INTERACTIONS

The 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 Fludeoxyglucose F 18 Injection and the gestational timing of exposure. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of 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 visualization 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 developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fludeoxyglucose F 18 Injection, any potential adverse effects on the breastfed child from Fludeoxyglucose F 18 Injection or from the underlying maternal condition.

## Clinical Considerations

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

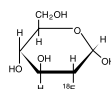
## 8.4 Pediatric Use

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

## 11 DESCRIPTION

### 11.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose has the molecular formula of C<sub>6</sub>H<sub>11</sub><sup>18</sup>FO<sub>5</sub> with a molecular weight of 181.26, and has the following chemical structure:



Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.40GBq (20.0 to 200 mCi) of 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

### 11.2 Physical Characteristics

Fluorine F 18 has a physical half-life of 109.7 minutes and decays to Oxygen O 16 (stable) by positron decay. The principal photons useful for imaging are the dual 511 keV "annihilation" gamma photons, that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 2).

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

Radiation/Emission	% Per Disintegration	Mean Energy
Positron (β <sup>+</sup> )	96.73	249.8 keV
Gamma (γ)*	193.46	511.0 keV

\*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-1 1026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 R/hr/mCi (1.35 × 10<sup>-6</sup> Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb). The range of attenuation coefficients for this radionuclide as a function of lead shield thickness is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

**Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding**

Shield thickness (Pb) mm	Coefficient of attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.

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

Minutes	Fraction Remaining
0*	1.000
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250

\*calibration time

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Fludeoxyglucose F 18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [<sup>18</sup>F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. F 18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

## 12.2 Pharmacodynamics

Fludeoxyglucose F 18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these 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 seizure focus tends to be hypometabolic.

## 12.3 Pharmacokinetics

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

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

**Metabolism:** Fludeoxyglucose F 18 is transported into cells and phosphorylated to [ $^{18}$ F]-FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [ $^{18}$ F]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[ $^{18}$ F]fluoro-6-phospho-D-mannose([ $^{18}$ F]FDM-6-phosphate).

Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (CIDG)). Biodistribution and metabolism of CIDG are presumed to be similar to Fludeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (CIDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (CIDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, CIDG, and CIDM) presumably leave cells by passive diffusion. Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose F 18 that is not involved in glucose metabolism in any tissue is then excreted in the urine.

**Elimination:** Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Within 33 minutes, a mean of 3.9% of the administered radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

### **Special Populations:**

The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in renally-impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained [see **Warnings and Precautions** (5.2)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the Fludeoxyglucose F 18 Injection carcinogenic potential, mutagenic potential or effects on fertility.

## 14 CLINICAL STUDIES

### 14.1 Oncology

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fludeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq.

In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false-positive scans. The efficacy of Fludeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

### 14.2 Cardiology

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects).

Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on 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 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 subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

### 16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL glass vial containing between 0.740 to 7.40 GBq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-2-[ $^{18}$ F]-fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 40028-511-30; 40028-511-50

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

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

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

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

### 17 PATIENT COUNSELING INFORMATION

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

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

Pregnancy: Advise pregnant women of the risk of fetal exposure to radiation with Fludeoxyglucose F 18 Injection [see **Use in Specific Populations** (8.1)].

Lactation: Advise lactating women that exposure to Fludeoxyglucose F 18 Injection through breast milk can be minimized by pumping and discarding breast milk and avoiding close (breast) contact with the infant for 9 hours after Fludeoxyglucose F 18 Injection [see **Use in Specific Populations** (8.2)].

### Manufactured and distributed by:

PETNET Solutions, Inc.  
810 Innovation Drive  
Knoxville, TN 37932

## PETNET Solutions

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**Siemens Healthineers AG**  
Siemensstr. 3  
91301 Forchheim  
Germany  
Phone: +49 9191 18-0  
siemens-healthineers.com

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810 Innovation Drive  
Knoxville, TN 37932  
USA  
Phone: +1 877 473 8638  
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