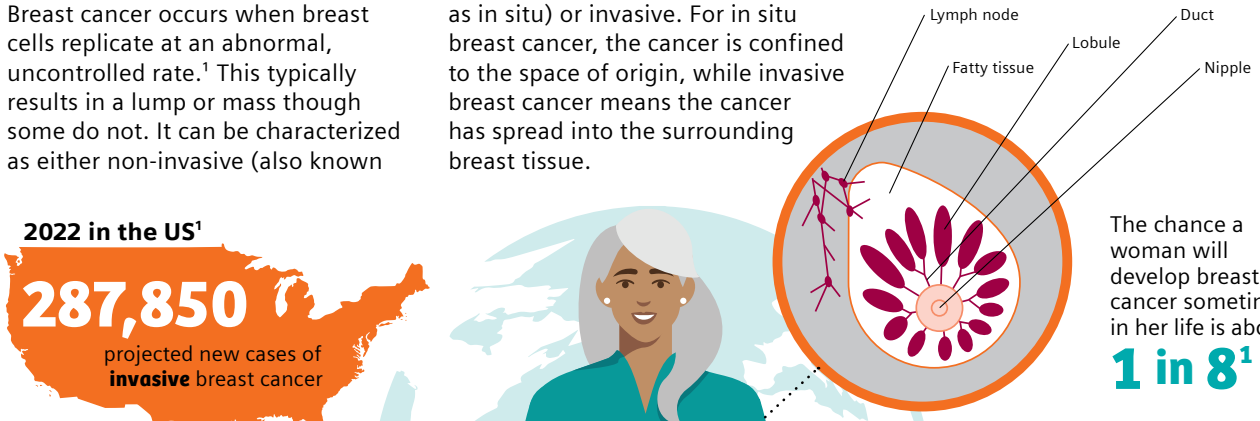
Breast cancer fact sheet

Breast cancer occurs when breast cells replicate at an abnormal, uncontrolled rate.[1] This typically results in a lump or mass though some do not. It can be characterized as either non-invasive (also known as in situ) or invasive. For in situ breast cancer, the cancer is confined to the space of origin, while invasive breast cancer means the cancer has spread into the surrounding breast tissue.



2022 in the US[1]

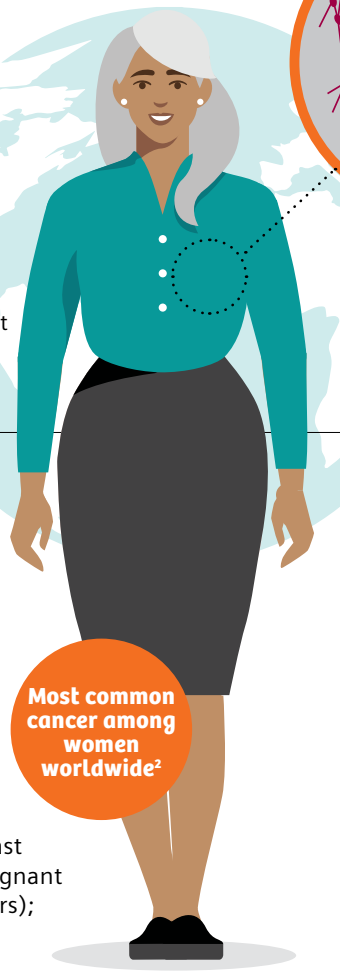
287,850
projected new cases of **invasive** breast cancer

43,250
estimated US deaths in 2022[1]

~1% of all breast cancer cases occur in men[3]

The chance a woman will develop breast cancer sometime in her life is about **1 in 8[1]**

About **51,400 new cases** of ductal carcinoma in situ will be diagnosed[1]



Types of breast cancer[4]

Adenocarcinomas (most common):
- Ductal (originating from milk ducts): either ductal carcinoma in situ (DCIS) or invasive ductal carcinoma
- Lobular (originating from milk-producing lobules): either lobular carcinoma in situ (LCIS) or invasive lobular

Less common breast cancers
- Inflammatory: Rare (up to ~5% of breast cancers) but aggressive
- Phylloides tumors: Rare (up to ~3% of breast cancers); 1 in 4 phylloides tumors are malignant
- Angiosarcomas: Rare (<1% of breast cancers); originates in blood or lymph vessels

Breast cancer molecular profile

Breast cancer is also differentiated based on receptor status:
- Estrogen and progesterone hormone receptors (ER/PR positive or negative)
- HER-2/neu positive or negative

Has treatment and prognostic implications:
- Hormone and HER-2/neu receptor-positive breast cancers are more amenable to hormonal and anti-HER2/neu therapy agents
- Hormone receptor-positive, HER-2/neu receptor-negative breast cancers have better prognosis than hormone receptor-negative, HER-2/neu receptor-positive breast cancers

Risk factors[5]

Age > 50

Prior family and/or personal history

Genetic mutations (BRCA1/BRCA2)

Prolonged hormonal exposure
- Start of menses age < 12 years old, menopause age > 55 years old
- Hormonal therapy/ Oral contraceptive

Reproductive history
- First gestation after age 30, or non-full term
- Non-breastfeeding

Screening recommendations[6]

1. Recommendations widely vary. Refer to the following table for further detail. https://www.cdc.gov/cancer/breast/pdf/breast-cancer-screening-guidelines-508.pdf
2. Self-breast awareness
   - Familiarity with look and feel of breasts to note when there is change
   - Any changes should be reported to healthcare provider

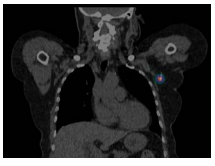
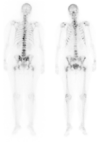
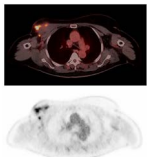
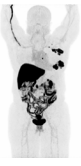
SIEMENS Healthineers

Diagnostic work-up and treatment[7,8,9]

	In situ cancer		Invasive cancer
	LCIS	DCIS*	
Diagnosis	History/physical Diagnostic mammogram Biopsy/path review	History/physical Diagnostic mammogram Biopsy/path review Molecular profile	History/physical Diagnostic mammogram Biopsy/path review Molecular profile +/- additional testing/imaging*
Treatment	No treatment (risk assessment, surveillance) Hormonal therapy Lumpectomy Prophylactic mastectomy	Lumpectomy vs mastectomy with/out SLN+ biopsy with/out radiation therapy with/out endocrine therapy	+/- Neoadjuvant chemotherapy* Lumpectomy vs mastectomy with axillary staging* Adjuvant radiation therapy +/- chemotherapy*

* based on multiple factors (i.e. stage, molecular profile, etc.) + sentinel lymph node

Molecular imaging for breast cancer

	Planar +/- SPECT, SPECT/CT		PET/CT		
	Lympho-scintigraphy	Whole-body bone imaging	Metabolic imaging	Whole-body bone imaging	Estrogen receptor status imaging
When?	Prior to breast surgery	In invasive cancers with bone pain or elevated serum alkaline phosphatase levels	In locally-advanced or metastatic disease	In invasive cancers with bone pain or elevated serum alkaline phosphatase levels	CERIANNA PET/CT imaging is indicated for the detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.
Why? Benefits	Sentinel lymph node identification precludes full axillary nodal dissection in all patients	Whole-body evaluation of osseous disease in appropriate patients	Evaluation of equivocal lesions, identification of regional nodal or distant metastatic disease[10]	Whole-body evaluation of osseous disease in appropriate patients	Detection of whole-body ER+ lesions may inform clinical decisions, including therapy selection
What? Radiotracer	^{99m}Tc sulfur colloid/ nanocolloid, ^{99m}Tc-tilmanocept	^{99m}Tc MDP/DPD/HDP	Fludeoxyglucose F 18 Injection (^{18}F FDG)**	Sodium Fluoride F 18 Injection (^{18}F NaF)***	Cerianna™ Fluoroestradiol F18 injection (^{18}F FES)****
Image examples	 Click to view	 Click to view	 Click to view	 Click to view	 Click to view
	Image courtesy of Chatham-Kent Health Alliance, Ontario, Canada.	Image courtesy of University of Tennessee Medical Center, Knoxville, TN, USA.	Image courtesy of Research Institute for Brain and Blood Vessels-Akita, Japan.	Image courtesy of Centre Hospitalier Princesse Grace, Monaco.	Image courtesy of 210 PET Imaging, Cary, NC, USA.

** Please see Indications and Important Safety Information for Fludeoxyglucose F 18 (^{18}F FDG) Injection on page 3. For full Prescribing Information, please see pages 6-17.

*** Please see Indications and Important Safety Information for Sodium Flouride F 18 (^{18}F NaF) Injection on page 3. For full Prescribing Information, please see pages 18-26.

**** Please see Indications and Important Safety Information for Cerianna™ (fluoroestradiol F 18) injection on page 4. For full Prescribing Information, please see pages 27-36.

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 functionin 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 pediatricpatients. 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.

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.

Sodium Fluoride F 18 Injection

INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection (^{18}F NaF) is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging bone to define areas of altered osteogenic activity.

IMPORTANT SAFETY INFORMATION

- **Allergic Reactions:** As with any injectable drug, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.
- **Cancer Risk:** Sodium Fluoride F 18 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker
- **Adverse Reactions:** No adverse reactions have been reported based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. The completeness of the sources is not known.

DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370 7,400 MBq/mL (10 200 mCi/mL) of no-carrier-added sodium fluoride F 18 at EOS reference time in aqueous 0.9% sodium chloride solution. Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-freesolution for intravenous administration.

Sodium Fluoride F 18 Injection is manufactured by Siemens' PETNET Solutions, 810 Innovation Drive, Knoxville, TN 39732

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 ERpositive 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 injectionsite 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 on next page

Drug interactions

Systemic endocrine therapies that target estrogen receptors

Certain classes of systemic endocrine therapies, including ER modulators and ER downregulators, 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 Zionexa US Corp at +1800.654.0118 or FDA at 1-800-FDA-1088 or 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 ^{18}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

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 (96.2 MBq) 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 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 (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.

----------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*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Oncology

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

1.2 Cardiology

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

1.3 Neurology

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

2 DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. 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[2] data and using the data published by the International Commission on Radiological Protection[4] for Fludeoxyglucose ^{18}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[a]

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[b]	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

[a] MIRDOSE 2 software was used to calculate the radiation absorbed dose.
[b] 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 Fludeoyxglucose 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

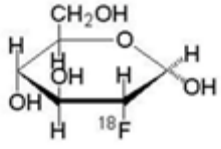
The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight 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-[^{18}F]fluoro-D-glucose has the molecular formula of $C_6H_{11}{}^{18}FO_5$ 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 7.40 GBq (20.0 to 200 mCi) of 2-deoxy-2-[^{18}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+)	96.73	249.8 keV
Gamma(±)*	193.46	511.0 keV

*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-I 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 x 10^{-6} 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 [^{18}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. Fludeoxyglucose F 18 is used to assess glucose metabolism.

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

12.2 Pharmacodynamics

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

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

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the 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 in duration, 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 (±) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 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 (ClDG)). Biodistribution and metabolism of ClDG 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 (ClDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, ClDG, and ClDM) 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 administrated 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

SODIUM FLUORIDE F 18- sodium fluoride f-18 injection, solution
PETNET Solutions, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Sodium Fluoride F 18 Injection safely and effectively. See full prescribing information for Sodium Fluoride F 18 Injection.
SODIUM FLUORIDE F 18 INJECTION
For Intravenous Use
Initial U.S. Approval: January 2011

INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging of bone to define areas of altered osteogenic activity (1).

DOSAGE AND ADMINISTRATION

- Sodium Fluoride F18 Injection emits radiation and must be handled with appropriate safety measures (2.1).
- Administer 300-450 MBq (8–12 mCi) as an intravenous injection in adults (2.4).
- Administer approximately 2.1 MBq/kg in children with a minimum of 19 MBq (0.5 mCi) and a maximum of 148 MBq (4 mCi) as an intravenous injection (2.5).
- Imaging can begin 1–2 hours after administration; optimally at one hour post administration (2.7).
- Encourage patients to void immediately prior to imaging the lumbar spine and bony pelvis (2.7).

DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) of no-carrier-added sodium fluoride F18 at the end of synthesis (EOS) reference time in aqueous 0.9% sodium chloride solution (3). Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Allergic Reactions: As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available (5.1).
- Cancer Risk: Sodium Fluoride F 18 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker (5.2).

ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems (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.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Any radiopharmaceutical, including Sodium Fluoride F18 injection, may cause fetal harm. Use only if clearly needed (8.1)
- Nursing: A decision should be made whether to interrupt nursing after Sodium Fluoride F 18 Injection administration or not to administer Sodium Fluoride F 18 Injection taking into consideration the importance of the drug to the mother. (8.3)
- Pediatrics: Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection (8.4).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

- Wear waterproof gloves and effective shielding when handling Sodium Fluoride F 18 Injection. Use

appropriate safety measures, including shielding, consistent with proper patient management 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.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Sodium Fluoride F 18 Injection.
- The dose of Sodium Fluoride F 18 Injection should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.
- The final dose for the patient should be calculated using proper decay factors from the time of End of Synthesis (EOS), and measured by a suitable radioactivity calibration system before administration *[see Description (11.2)]*.

2.2 Radiation Safety - Patient Preparation

- To minimize the radiation-absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to ingest at least 500 mL of fluid immediately prior and subsequent to the administration of Sodium Fluoride F 18 Injection.
- Encourage the patient to void one-half hour after administration of Sodium Fluoride F 18 Injection and as frequently thereafter as possible for the next 12 hours.

2.3 Drug Preparation and Administration

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

2.4 Recommended Dose for Adults

Administer 300–450 MBq (8–12 mCi) as an intravenous injection.

2.5 Recommended Dose for Pediatric Patients

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi–4 mCi) were used.

2.6 Radiation Dosimetry

The age/weight- based estimated absorbed radiation doses (mGy/MBq) from intravenous injection of Sodium Fluoride F 18 Injection are shown in Table 1. These estimates were calculated based on human data and using the data published by the Nuclear Regulatory Commission [1] and the International Commission on Radiological Protection for Sodium Fluoride Injection [2]. The bone, bone marrow and urinary bladder are considered target and critical organs.

Table 1: Estimated Absorbed Radiation Doses after Intravenous Administration of Sodium Fluoride F 18 Injection

Organ	Estimated Radiation Dose mGy/MBq				
	Adult 70 kg [1]	15 year 56.8 kg [2]	10 year 33.2 kg [2]	5 year 19.8 kg [2]	1 year 9.7 kg [2]
Adrenals	0.0062	0.012	0.018	0.028	0.052

Brain		0.0056	N/A	N/A	N/A	N/A
Bone surfaces		0.060	0.050	0.079	0.13	0.30
Breasts		0.0028	0.0061	0.0097	0.015	0.030
GI	Gallbladder wall	0.0044	N/A	N/A	N/A	N/A
	Stomach wall	0.0038	0.008	0.013	0.019	0.036
	Small intestine	0.0066	0.012	0.018	0.028	0.052
	Upper large intestine wall	0.0058	0.010	0.016	0.026	0.046
	Lower large intestine wall	0.012	0.016	0.025	0.037	0.063
Heart wall		0.0039	N/A	N/A	N/A	N/A
Kidneys		0.019	0.025	0.036	0.053	0.097
Liver		0.0040	0.0084	0.013	0.021	0.039
Lungs		0.0041	0.0084	0.013	0.020	0.039
Muscle		0.0060	N/A	N/A	N/A	N/A
Ovaries		0.011	0.016	0.023	0.036	0.063
Pancreas		0.0048	0.0096	0.015	0.023	0.044
Red marrow		0.028	0.053	0.088	0.18	0.38
Skin		0.0040	N/A	N/A	N/A	N/A
Spleen		0.0042	0.0088	0.014	0.021	0.041
Testes		0.0078	0.013	0.021	0.033	0.062
Thymus		0.0035	N/A	N/A	N/A	N/A
Thyroid		0.0044	0.0084	0.013	0.020	0.036
Urinary bladder wall		0.25	0.27	0.4	0.61	1.1
Uterus		0.019	0.023	0.037	0.057	0.099
Other tissue		N/A	0.010	0.015	0.024	0.044
Effective Dose Equivalent mSv/MBq		**0.027**	**0.034**	**0.052**	**0.086**	**0.17**

[1] Data from Nuclear Regulatory Commission Report, *Radiation Dose Estimates for Radiopharmaceuticals*, NUREG/CR-6345, page 10, 1996.

[2] Data from ICRP publication 53, *Radiation Dose to Patients from Radiopharmaceuticals* , Ann ICRP, Volume 18, pages 15 and 74, 1987

2.7 Imaging Guidelines

- Imaging of Sodium Fluoride F 18 Injection can begin 1–2 hours after administration; optimally at 1 hour post administration.
- Encourage the patient to void immediately prior to imaging the fluoride F18 radioactivity in the lumbar spine or bony pelvis.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7.400 MBq/mL (10–200 mCi/mL) at EOS reference time of no-carrier-added sodium fluoride F18 in aqueous 0.9% sodium chloride solution. Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.

5.2 Radiation Risks

Sodium Fluoride F 18 Injection may increase the risk of cancer. Carcinogenic and mutagenic studies with Sodium Fluoride F18 injection have not been performed. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Any radiopharmaceutical including Sodium Fluoride F 18 Injection has a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the radionuclide dose. Animal reproductive and developmental toxicity studies have not been conducted with Sodium Fluoride F 18 Injection. Prior to the administration of Sodium Fluoride F 18 Injection to women of childbearing potential, assess for presence of pregnancy. Sodium Fluoride F 18 Injection should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Sodium Fluoride F 18 Injection is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to interrupt nursing after administration of Sodium Fluoride F 18 Injection or not to administer Sodium Fluoride F 18 Injection, taking into account the importance of the drug to the mother. The body of scientific information related to radioactivity decay, drug tissue distribution and drug elimination shows that less than 0.01% of the radioactivity administered remains in the body after 24 hours (10 half-lives). To minimize the risks to a nursing infant, interrupt nursing for at least 24 hours.

8.4 Pediatric Use

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi - 4 mCi) were used. Sodium Fluoride F18 was shown to localize to areas of bone turnover including rapidly growing epiphyses in developing long bones.

Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection.

11 DESCRIPTION

11.1 Chemical Characteristics

Sodium Fluoride F 18 Injection is a positron emitting radiopharmaceutical, containing no-carrier-added, radioactive fluoride F18 that is used for diagnostic purposes in conjunction with PET imaging. It is administered by intravenous injection. The active ingredient, sodium fluoride F18, has the molecular formula Na[^{18}F] with a molecular weight of 40.99, and has the following chemical structure:

$Na^{+}\ {}^{18}F^{-}$

Sodium Fluoride F 18 Injection is provided as a ready-to-use, isotonic, sterile, pyrogen-free, preservative-free, clear and colorless solution. Each mL of the solution contains between 370 MBq to 7,400 MBq (10 mCi to 200 mCi) sodium fluoride F18, at the EOS reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8. The solution is presented in 30 mL multiple- dose glass vials with variable total volume and total radioactivity in each vial.

11.2 Physical Characteristics

Fluoride F18 decays by positron (β+) emission and has a half-life of 109.7 minutes. Ninety-seven percent of the decay results in emission of a positron with a maximum energy of 633 keV and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 2). Fluorine F18 atom decays to stable ^{18}O-oxygen.

Table 2: Principal Emission Data for Fluoride F18

Radiation/Emission	% per Disintegration	Mean Energy
Positron (β+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

* Produced by positron annihilation

[3] Kocher, D.C. Radioactive Decay Data Tables DOE/TIC-11026, 69, 1981.

The specific gamma ray constant for fluoride F18 is 5.7 R/hr/mCi (1.35×10^{-6} Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). A range of values for the attenuation of radiation results from the interposition of various thickness of Pb. The range of attenuation coefficients for this radionuclide is shown in Table 3. For example, the interposition of an 8.3 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

Table 4 lists the fraction of radioactivity remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4: Physical Decay Chart for Fluoride F18

Time Since Calibration	Fraction Remaining
0*	1.00
15 minutes	0.909
30 minutes	0.826
60 minutes	0.683
110 minutes	0.500
220 minutes	0.250
440 minutes	0.060
12 hours	0.011
24 hours	0.0001

* Calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluoride F18 ion normally accumulates in the skeleton in an even fashion, with greater deposition in the axial skeleton (e.g. vertebrae and pelvis) than in the appendicular skeleton and greater deposition in the bones around joints than in the shafts of long bones.

12.2 Pharmacodynamics

Increased fluoride F18 ion deposition in bone can occur in areas of increased osteogenic activity during growth, infection, malignancy (primary or metastatic) following trauma, or inflammation of bone.

12.3 Pharmacokinetics

After intravenous administration, fluoride F18 ion is rapidly cleared from the plasma in a biexponential manner. The first phase has a half-life of 0.4 h, and the second phase has a half-life of 2.6 h. Essentially all the fluoride F18 that is delivered to bone by the blood is retained in the bone. One hour after administration of fluoride, F18 only about 10% of the injected dose remains in the blood. Fluoride F18 diffuses through capillaries into bone extracellular fluid space, where it becomes bound by chemisorption at the surface of bone crystals, preferentially at sites of newly mineralizing bone.

Deposition of fluoride F18 in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the fluoride F18. Fluoride F18 does not appear to be bound to serum proteins.

In patients with normal renal function, 20% or more of the fluorine ion is cleared from the body in the urine within the first 2 hours after intravenous administration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess reproductive toxicity, mutagenesis and carcinogenesis potential of Sodium Fluoride F 18 Injection have not been performed.

14 CLINICAL STUDIES

14.1 Metastatic Bone Disease

The doses used in reported studies ranged from 2.7 mCi to 20 mCi (100 MBq to 740 MBq), with an average median dose of 10 mCi (370 MBq) and an average mean dose of 9.2 mCi (340 MBq). In PET imaging of bone metastases with Sodium Fluoride F 18 Injection, focally increased tracer uptake is seen in both osteolytic and osteoblastic bone lesions. Negative PET imaging results with Sodium Fluoride F 18 Injection do not preclude the diagnosis of bone metastases. Also, as benign bone lesions are also detected by Sodium Fluoride F 18 Injection, positive PET imaging results cannot replace biopsy to confirm a diagnosis of cancer.

14.2 Other Bone Disorders

The doses used in reported studies ranged from 2.43 mCi to 15 mCi (90 MBq to 555 MBq), with an average median dose of 8.0 mCi (300 MBq) and an average mean dose of 7.6 mCi (280 MBq).

15 REFERENCES

1. Stabin, M.G., Stubbs, J.B. and Toohey R.E., Radiation Dose Estimates for Radiopharmaceuticals, U.S. Nuclear Regulatory Commission report NUREG/CR-6345, page 10, 1996.
2. Radiation Dose to Patients from Radiopharmaceuticals, ICRP publication 53, Ann ICRP, 18 pages 15 and 74, 1987
3. Kocher, D.C., "Radioactive Decay Data Tables: A Handbook of decay data for application to radiation dosimetry and radiological assessments" DOE/TIC-11026, page 69, 1981.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sodium Fluoride F 18 Injection is supplied in a multiple-dose Type I glass vial with elastomeric stopper and aluminum crimp seal containing between 370 and 7,400 MBq/mL (10–200 mCi/mL) of no carrier-added sodium fluoride F18, at the EOS reference time, in aqueous 0.9% sodium chloride solution. The total volume and total radioactivity per vial are variable. Each vial is enclosed in a shielded container of appropriate thickness.

The product is available in a 30 mL vial configuration with a variable fill volume. The NDC number is:

40028-512-30 (30 mL)

Storage

Store at 25°C (77°F) in a shielded container; excursions permitted to 15–30°C (59–86°F). Use the solution within 12 hours of the EOS reference time.

Handling

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.

17 PATIENT COUNSELING INFORMATION

17.1 Pre-study Hydration

Encourage patients to drink at least 500 mL of water prior to drug administration.

17.2 Post-study Voiding

To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible, use a toilet and flush several times after each use; wash hands thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, wash the clothing separately.

Manufactured by:

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810 Innovation Drive
Knoxville, TN 37932

Distributed by:

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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

To report SUSPECTED ADVERSE REACTIONS, contact Zionexa US Corp at +1.800.654.0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

----------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:03/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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 (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

Table 1. Estimated Radiation Absorbed Doses in Various Organs/Tissues in Adults Who Received FLUOROESTRADIOL F 18	
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 1207 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 2-4% and 15-20%, 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.

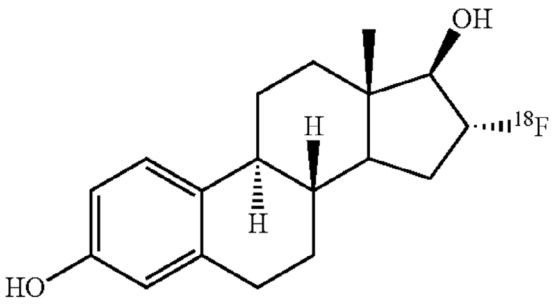
8.5 Geriatric Use

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]16α-fluoro-3,17β-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 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

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 x 10^{-17} 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 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: Kd = 0.13 ± 0.02 nM, Bmax = 1901 ± 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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