CERIANNA™ (fluoroestradiol F 18) Injection

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

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

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

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

DOSE 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 administration. (2.4)
- See full prescribing information for additional preparation, administration, imaging, and radiation dosimetry information. (2)

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

RISKS OF MISDIAGNOSIS
Do not use CERIANNA if a radiotracer is not found in the tissue of interest. Do not use CERIANNA if there is a suspicion of metastatic disease or if the radiotracer is not found in the tissue of interest.

RADIATION RISKS
- Radiation Risks. Ensure safe drug handling procedures and radiation shieldings, when preparing and handling CERIANNA. Use waterproof gloves and effective radiation shielding, including syringe shields, when preparing and handling CERIANNA. (5.2)
- Radiation Risks. Effective dose = 0.022 mSv/MBq

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

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

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

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 in a multiple-dose vial.
8.4 Pediatric Use
Clinical studies of fluoroestradiol F 18 injection did not reveal any difference in pharmacokinetics or biodistribution in patients aged 65 and over.

8.1 Pregnancy
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
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.

8.3 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)].

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

9 DRUG INTERACTIONS

11.3 External Radiation
The point source air-kerma coefficient for F 18 is 3.75 x 10^-1 Gy m^2 J^-1 (Rg 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.

11 DESCRIPTION

11.1 Chemical Characteristics
CERIANNA contains fluoroestradiol flurine 18 (F 18), a synthetic estrogen analog. Chemically, fluoroestradiol F 18 is [{\textsuperscript{18}F}]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 osmolality of 330 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>
<thead>
<tr>
<th>Radiation</th>
<th>Energy Level (keV)</th>
<th>% Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position</td>
<td>249.8</td>
<td>96.9</td>
</tr>
<tr>
<td>Gamma</td>
<td>511</td>
<td>193.5</td>
</tr>
</tbody>
</table>

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

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

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

12 CLINICAL PHARMACOLOGY

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

12.2 Pharmacodynamics
The relationship between fluoroestradiol 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

<table>
<thead>
<tr>
<th>Distribution</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>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.</td>
</tr>
<tr>
<td>Excretion</td>
<td>Elimination is by biliary and urinary excretion.</td>
</tr>
</tbody>
</table>
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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 typhiurium 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 10 hours from the time of the end of synthesis.

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

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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