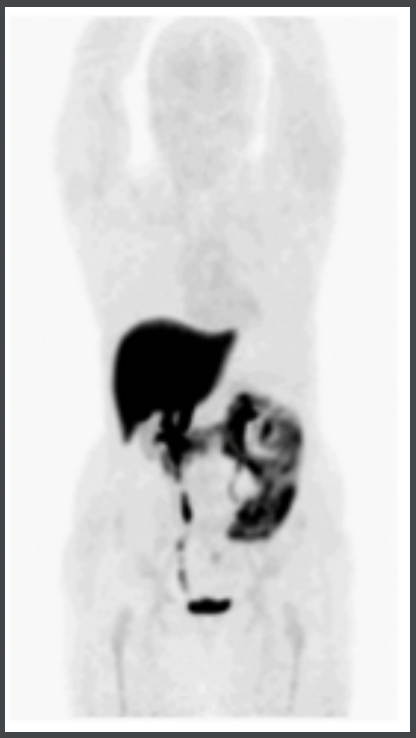
User's guide

cERianna™

(FLUOROESTRADIOL F 18) INJECTION

Clinical uses for Cerianna
148-3700 MBq/mL
Solution for injection



Physiologic uptake of Cerianna™ PET/CT

Z.US0007 V1.00

Contents

Indication and important safety information

Indication 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).

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

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

To see full prescribing information, please visit www.cerianna.com

Safety and specific populations

Safety

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

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

Use in specific populations

Pregnancy & Lactation

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.

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.

Advise a pregnant woman of the potential risks of fetal exposure to radiation from administration of Cerianna.

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.

Storage and Handling

Storage

Store Cerianna Injection 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.

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. Use waterproof gloves and effective radiation shielding, including syringe shields, when preparing and handling Cerianna.

Recommended dosing and administration

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. Dosage is according to the body weight of the patient, the type of camera used and the acquisition mode.

Radiation dosimetry

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.

Patient preparation

- 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.
- Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with Cerianna.
- Advise a lactating woman to avoid breastfeeding for 4 hours after Cerianna administration in order to minimize radiation exposure to a breastfed infant.
- Assessment of pregnancy status is recommended in females of reproductive potential before administering Cerianna.
- No fasting is required

Recommended best practices

- Assay the dose in a suitable dose calibrator prior to administration.
- Use aseptic technique and radiation shielding when withdrawing and administering Cerianna.
- Visually inspect Cerianna solution. Do not use if it contains particulate matter or if it is cloudy or discolored.
- Cerianna may be diluted with 0.9% Sodium Chloride Injection, USP, when the dose is prepared and just before injected the patient
- Inject Cerianna on the contralateral arm of the primary tumor
- After the Cerianna injection, administer an intravenous flush of sterile Sodium Chloride Injection, 0.9% to ensure full delivery of the dose.
- Dispose of any unused Cerianna in compliance with applicable regulations.

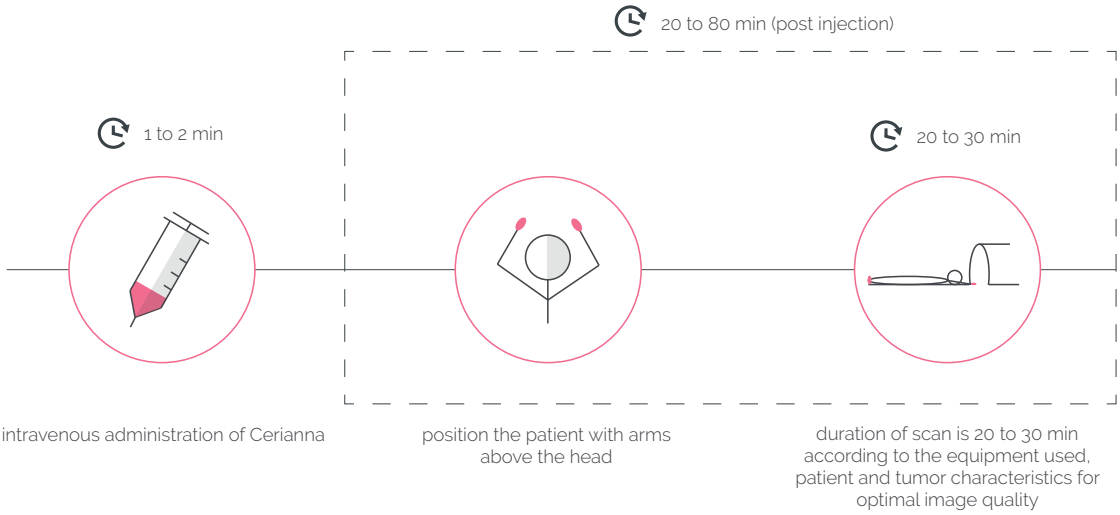
Dosage forms and strengths

Injection: clear, colorless solution in a 50 mL multiple-dose vial containing 148-3700 MBq/mL (4 to 100 mCi/mL) of Fluoroestradiol F 18 at end of synthesis. It is enclosed in a shield container to minimize external radiation exposure

Image acquisition guidelines

Image acquisition guidelines

• The recommended start time for image acquisition is 80 minutes (20 minutes to 80 minutes) after the intravenous administration of Cerianna
• Position the patient supine with arms above the head, if possible. Scanning should include entire area from knee to the top of the skull
• Duration of scan is 20 to 30 minutes according to the equipment used and patient and tumor characteristics for optimal image quality



• Basic processing parameters should follow the guidelines of SNMMI Procedure Standards called FDG PET/CT: EANM procedure guidelines for tumour imaging.

Pitfalls

Image shows the physiologic uptake of Cerianna will be found in estrogen producing organs (i.e., ovary, uterus), in liver (metabolization site) and in elimination site (biliary and urinary excretion.).
As 18F-FES is metabolized by the liver, liver lesions cannot be assessed.

If scanning is started earlier than 20 minutes, 18F-FES may not be distributed in all organs due to the fact that after injection, 18F-FES distributes primarily to hepatobiliary system, and also to small and large intestines, heart wall, blood, kidney, uterus and bladder.

If scanning is started later than 80 minutes, 18F-FES will be mostly metabolized, given that 2 hours after injection, circulating 18F-FES levels are less than 5% of peak concentration.

Image display and interpretation

• Uptake of 18F-FES depends on ER density and binding function in tumors and physiologic tissue, including in liver, ovary, and uterus. As a rule, all lesions with an uptake greater than background are considered as positive, i.e. evidence of the presence estrogen receptors ligand binding function of estrogen receptors

• 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

• Studies on 18F-FES have used SUV thresholds ranging from 1[1] through 1.8[2] for calling a lesion 18F-FES. Most commonly used threshold is 1.5.

• While quantitation is attractive, there are nuances within interpreting 18F-FES SUV values
  - o Background SUV values differ in various tissues[3]
  - o Recent treatment with ER antagonists may affect SUV values, therefore thresholds are unreliable
  - o Partial volume effect

• Therefore, Zionexa currently recommends avoiding 18F-FES scan interpretations solely based on SUV values.

References: [1] Peterson 2008, [2] Chae 2019, [3] Nienhuis 2018

Risk for misdiagnosis and drugs interactions

Risk of misdiagnosis

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

• *False Negative Cerianna Scan*
A negative Cerianna scan does not rule out ER-positive breast cancer. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative Cerianna scan.

Drug interactions

• 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

Therapy	Duration
ER modulator (e.g., tamoxifen, toremifene)	8 weeks
ER down-regulator (e.g., fulvestrant)	28 weeks

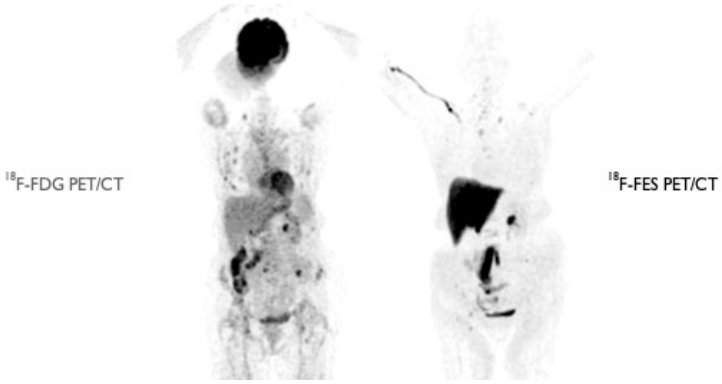
• Do not delay indicated therapy in order to administer Cerianna. Administer Cerianna prior to starting systemic endocrine therapies that block ER

Cerianna PET/CT: Heterogeneity (case 1/3)

History

• 67-year-old functional breast cancer patient with a history of invasive lobular cancer in the left breast, (ER)+, HER 2 -, with history of metastatic disease predominantly to the bones

The patient progressed within six months on hormonal therapy
• 18F-FDG and 18F-FES scan ordered to restage patient and assess for heterogeneity of ER expression



Conclusion

• Case illustrates the importance of stepping through both studies simultaneously. There is a very heterogenous distribution of ER expression compared to the FDG documented metastatic lesions

• Many lesions demonstrate ER expression and many show no over-expression of ER (ER-)

• Given the heterogenous nature of Patient's tumors this would explain her unresponsiveness to hormonal therapy
• Patient was changed to systemic chemotherapy

Cerianna PET/CT: Lobular breast cancer (case 2/3)

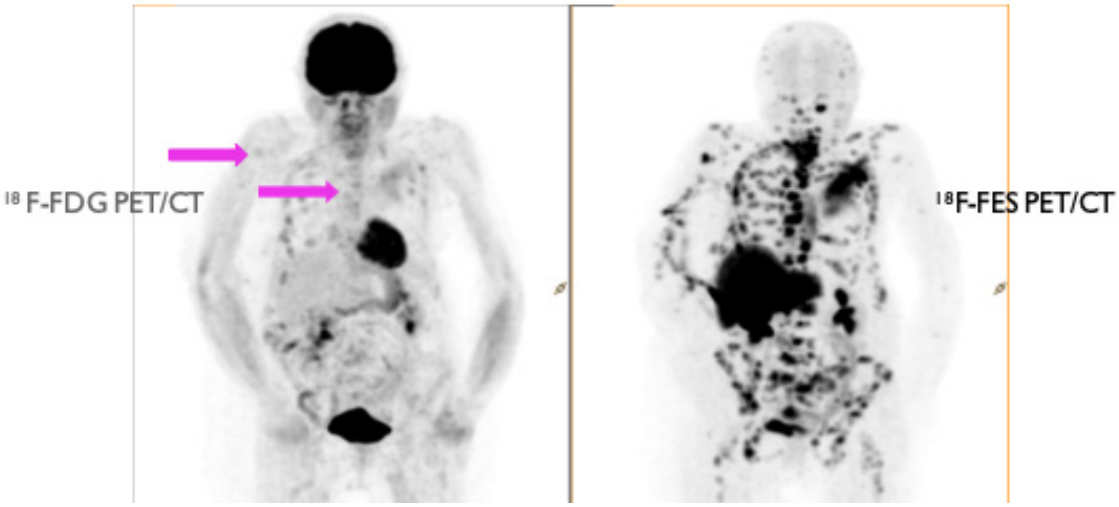
History

• Left breast lobular carcinoma estrogen receptor (ER)+, HER2, T2N0M0

• Treatment with neo-adjuvant chemotherapy, surgery, adjuvant chemotherapy, radiation therapy and hormone therapy (Tamoxifen) 5 years

• 8 years after treatment completion, emergence of vertebral fractures of T10 and T12

• CA 15-3 = 3500 U/mL (N<25)



Conclusion

• All lesions express ERs

• Higher accumulation of FES than FDG, probably because of the lobular histology

• Some lesions are barely seen with FDG (Pink arrows)

• Treatments by aromatase inhibitor (Exemestane), with lesions stabilization and CA 153 reduction (150 U/mL) 2 years after treatment beginning

Cerianna PET/CT: Problem solving tool (case 3/3)

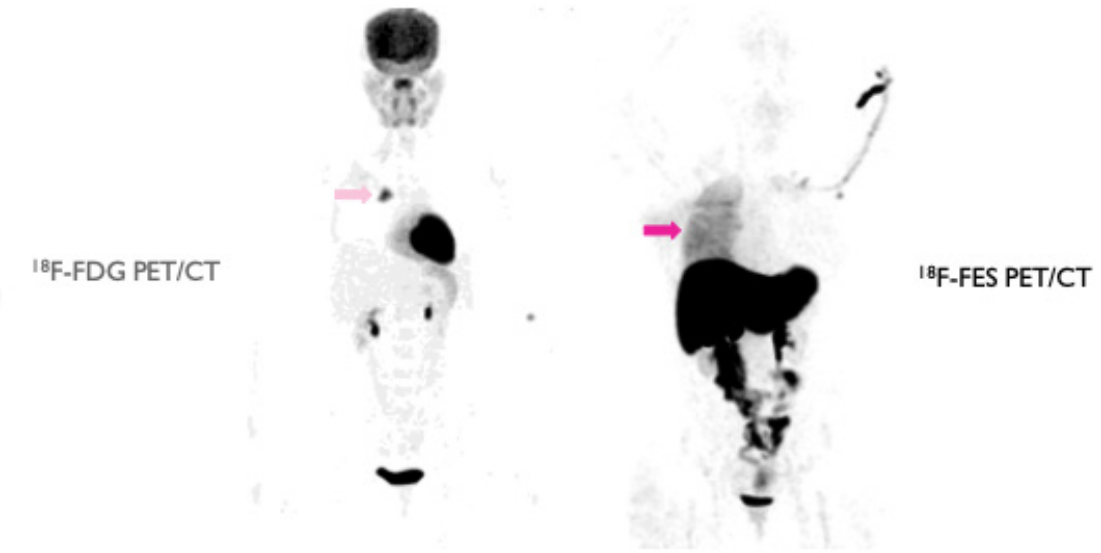
History

• 44-year-old female smoker with history of stage II breast cancer, (ER)+, (PR)+, HER2+ treated with definitive surgery, radiation and adjuvant hormonal therapy

• Now four years out from initial diagnosis and presents with abnormal fullness of right hilum

• ? Etiology - breast cancer, lung cancer or inflammatory

• 18F-FES and 18F-FDG ordered for problem solving utilization scenarios



Conclusion

• 18F-FDG PET/CT characterized lesion as hypermetabolic

• 18F-FES noted no over expression of estrogen receptors and no other lesions noted

• Patient sent to biopsy which revealed adenocarcinoma consistent with new early stage lung cancer (light pink arrow)

• Incidental finding - diffuse pulmonary uptake involving the right lung which can be seen after radiation therapy (dark pink arrow)

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Adverse Event Reporting: You are encouraged to report side effects of Cerianna Fluoroestradiol 18F by calling +1.844.946.6392. Suspected adverse reactions can also be reported directly to the FDA by visiting MedWatch or calling 1-800-FDA-1088.