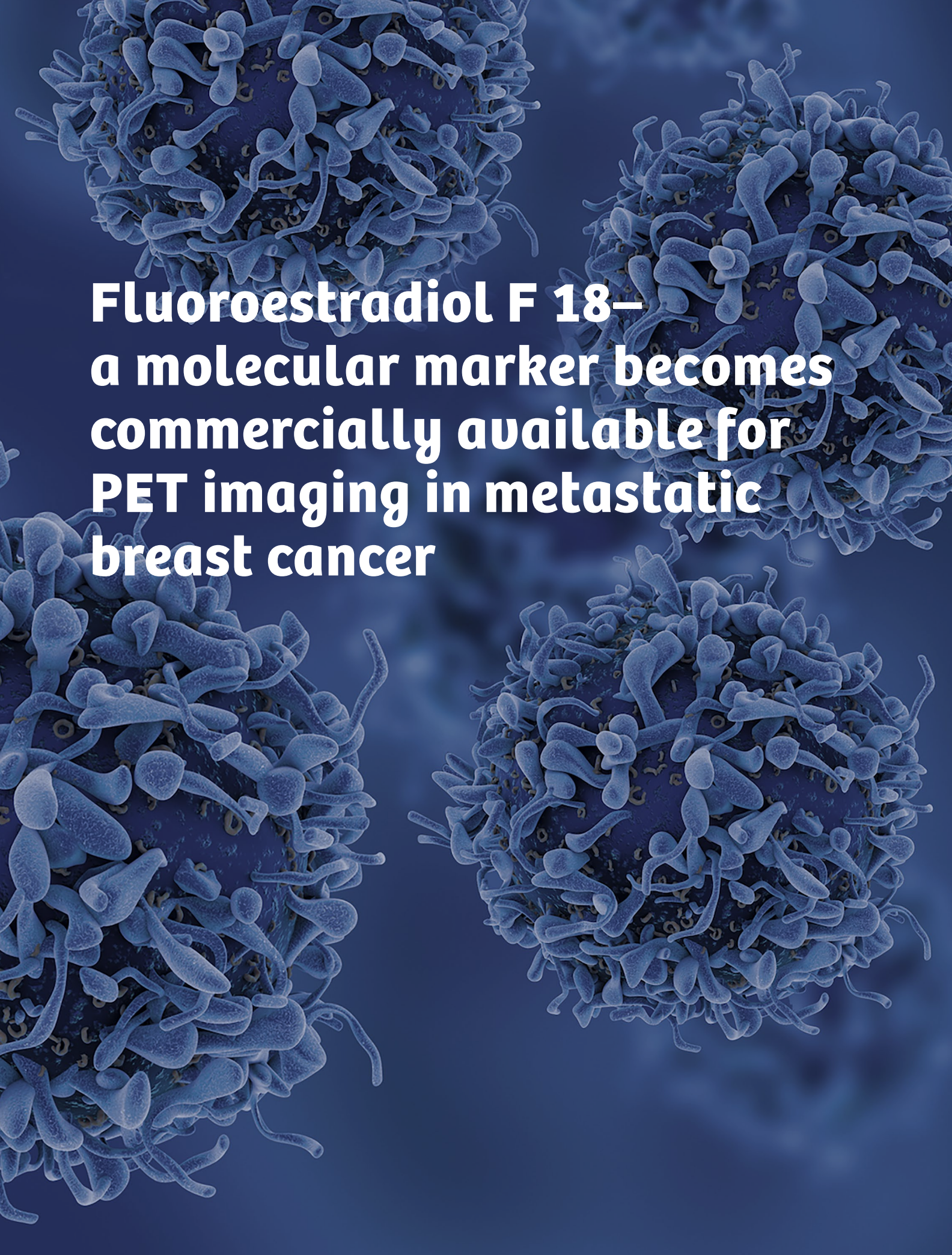


Fluoroestradiol F 18– a molecular marker becomes commercially available for PET imaging in metastatic breast cancer

On May 20, 2020, a new radiopharmaceutical agent was approved by the US Food and Drug Administration (FDA) for use with PET imaging: Fluoroestradiol F 18 (FES). Known in the US as Cerianna™, the radiopharmaceutical is an estrogen analog (16α-[^{18}F]-fluoro-17β-estradiol) and the first F-18 PET imaging agent to be indicated for the detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer (MBC).[1,2]

By Linda Brookes | Illustrations provided by Zionexa SAS

Cerianna was developed by Zionexa SAS (Paris, France) and is exclusively manufactured and distributed throughout the United States by PETNET Solutions, Inc., a Siemens Healthineers company (Knoxville, TN, USA). "Cerianna's approval is a huge milestone for patients with recurrent and metastatic breast cancer," says Peter Webner, CEO of Zionexa USA (New York, NY, USA). "It will soon be a tool available to help provide oncologists with a picture of the estrogen receptor expression. We can now image the whole body and provide information on ER status in many lesions, not just a single-biopsied lesion," he declares.

Determining ER status in MBC

ER status is important in breast cancer for risk assessment and predicting response to therapy. Both the US National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend ER testing of lesions in any primary or newly metastatic breast cancer.[3,4]

Approximately 75 percent of all breast cancers in women, and 99 percent in men, are ER-positive,[5,6] and almost all these patients will be candidates for endocrine therapies including selective estrogen receptor modulators (SERMs), selective estrogen receptor degraders (SERDs), aromatase inhibitors, and cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors. The outlook for MBC patients has changed tremendously with the introduction of these therapies, Webner notes. Between 1985 and 2016, median overall survival in women with MBC improved from 13 months to 33 months and 5-year survival increased from 10 percent to 27 percent.[7]

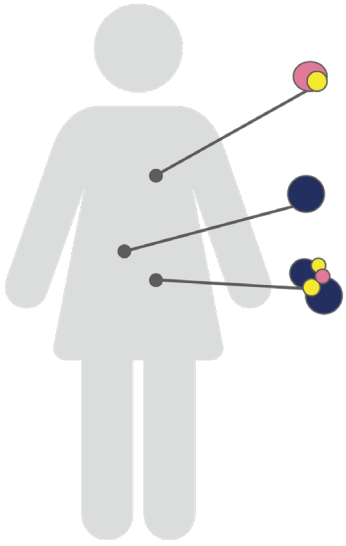
Despite the utility of endocrine therapy, ER discordance and inter-tumor heterogeneity likely contribute to low treatment response rates, Webner explains. Discordance in ER expression between the primary tumor and metastases occurs in about 20 percent of breast cancer patients.[8]

ER status may differ between metastatic lesions, and cancers that switch to low ER expression (around 20 percent) often have characteristics more similar to ER-negative cancers. These types of cancers are unlikely to respond to hormonally driven therapy, which has clinical and economic consequences, explains Yann Bouvet, PhD, CSO, at Zionexa SAS.

Peter Webner, CEO, Zionexa USA

Yann Bouvet, PhD, CSO, Zionexa SAS

What is ER heterogeneity in MBC?



Intra-tumor heterogeneity:
a single lesion may have ER+ and ER- disease

Inter-tumor heterogeneity:
two lesions may have different ER status from one another

Temporal heterogeneity:
ER status can change over time, especially following treatment

To date, the gold standard for determining ER status in MBC is immuno-histochemistry (IHC) on tissue biopsies from the primary tumor and usually a single metastasis, although most MBC patients have many metastases, most frequently in bone and lung. Obtaining tissue by biopsy can be particularly difficult at these sites and IHC is not used consistently in MBC patients, even if recommended by guidelines like those of the NCCN, Bouvet says. As a result, he maintains, treatment decisions are often based on incomplete and imperfect information. Another disadvantage of biopsy is that it is an invasive and painful exam, he notes.

COVID-19's impact to Cerianna's rollout

The phased roll-out of Cerianna to United States customers, scheduled to begin late 2020 or early 2021, is not expected to be affected by restrictions caused by the COVID-19 outbreak, according to Barry Scott. The PETNET Solutions team has been working with Zionexa to ensure pharmacies are operational and, despite some challenges, the plan for the launch remains unchanged, Scott says. "We have a good plan and should be able to stick with it," he confirms.

FES-PET versus Biopsy IHC

The use of FES in PET imaging (FES-PET) has many advantages for the clinician and patient, Bouvet stresses. The FES imaging agent is administered by intravenous injection and provides results within 24 hours of the exam, compared to two weeks with IHC. Importantly, unlike IHC, FES-PET can assess ER expression of every tumor in the body simultaneously, providing what Webner calls, "an ER status map of the whole body." FES-PET/CT can also distinguish between ER-positive and -negative lesions, which cannot be done with standard imaging.

FDA approval for Cerianna was based primarily on trial data that confirmed the diagnostic accuracy of FES-PET versus IHC[9] and the correlation of low FES uptake with lack of ER expression.[10] Analysis of ER status determined by FES-PET versus biopsy IHC showed an overall sensitivity and specificity of 83 percent on metastatic lesions and primary tumor.[11]

FES-PET is associated with acceptable levels of radiation exposure and a high safety profile with the potential for injection site pain and dysgeusia as the main side effects, occurring in less than one percent of patients. The primary consideration for FES-PET is the need for prior washout of drugs like tamoxifen or fulvestrant, which block the estrogen receptor and would impact the uptake of FES, Bouvet explains.

Cerianna™ (18F-FES)

Indications and Usage

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

Limitations of Use

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

Important Safety Information

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

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

Dosage and Administration

Dosage form and strengths

- Injection: clear, colorless solution in a multiple-dose vial containing 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of Cerianna at end of synthesis.

Patient preparation

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

Dosage and administration

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

Post administration

- Follow FES injection with an IV flush of 0.9% Sodium Chloride injection, USP

Safety of 18F-FES

Safety was determined from 1,207 patients with breast cancer receiving at least one Fluoroestradiol F18 administration

Age range = 21-91 years

- 98% were women
    - 76% were post-menopausal

Safety profile was based on clinical studies + NCI investigator's brochure:

- No serious adverse events
- Adverse events with <1% frequency
    - Injection site pain
    - Dysgeusia

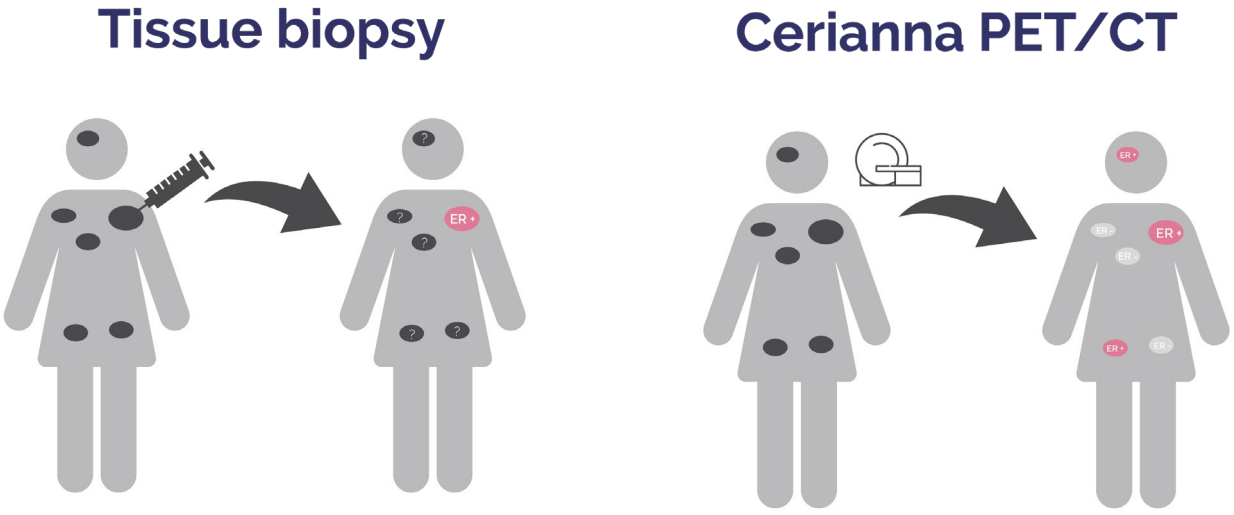
"New biomarkers just don't come around that often and this one, in particular, is highly attractive in the market today."

Barry Scott, CEO, PETNET Solutions

FES-PET-driven personalized medicine

"Our goal is to be able to help identify the patients that will best benefit from therapy," Webner stresses. "With FES-PET we can identify patients who have estrogen-driven disease versus the ones who don't, or the ones who have mixed disease. Then the clinician has actionable data with which they can make a therapeutic choice that should help them extend the patient's survival and hopefully give them a better outcome." When the options involve expensive drugs, the choice can also be cost effective, Webner adds. For example, patients with 100 percent FES positivity appear to benefit most from treatment with CDK4/6 inhibitors[12] and, "since they are not indicated for ER-negative disease, there's clear financial benefit in having the patient go on to an alternate therapy that will give better outcomes," Webner explains.

Zionexa aims to extend the indication for Cerianna by supporting what was observed in small populations during clinical trials to use it for early response to endocrine therapy. The IMP ACT-MBC (IMaging PAtients for Cancer Drug selecTion - Metastatic Breast Cancer) trial is looking at the clinical utility of experimental PET scans, including FES, in the setting of MBC at first presentation, and initial results appear promising.[13] Another multicenter clinical trial being carried out by the ECOG-ACRIN Cancer Research Group is evaluating the predictive value of FES in patients with newly diagnosed breast cancer.



New Era for an Old Concept

FES was first synthesized over 30 years ago[14] and has since been studied in breast cancer imaging worldwide, Webner recalls. The original formulation was stable for only 4-6 hours, and could only be produced in small batches. Zionexa was able to develop an industrial process and subsequently obtain a formulation with high-specific activity and an expiry period of 10-12 hours. The company was granted a patent for its formulation and process in July 2020.

"F-18 isotopes have a half-life of 110 minutes, so partnering with a world class organization like PETNET Solutions will be key to timely regional manufacturing and distribution throughout the country," Webner emphasizes. Barry Scott, CEO of PETNET Solutions, explains that with a network of 43 cyclotron-equipped pharmacies across the United States, PETNET Solutions can reach a broad spectrum of population in the nation, ensuring that hospitals and imaging centers have access to novel biomarkers like Cerianna.

New products are always challenging to launch, Webner observes. "Changing the way physicians practice is not a quick process and we need to work with oncologists to help them identify the correct patient profiles for this exam and with imagers to ensure they provide actionable information to the referring physicians," he states. "Since FES-PET is a type of receptor imaging, interpreting a Cerianna scan is different from most other PET tracers currently in use. An important step will be to have FES-PET included in national breast cancer management guidelines, which are key in breast cancer care," Webner adds.

Based on PETNET Solutions' commercial experience, Scott is optimistic about the future of Cerianna. "New biomarkers just don't come around that often and this one, in particular, is highly attractive in the market today," he declares. A phased US roll-out of Cerianna is set to begin by early 2021. ●

Linda Brookes, MSc, is a freelance medical writer and editor, dividing her time between London and New York, working for a variety of clients in the healthcare and pharmaceutical fields.

References

1 Zionexa US Corp. Cerianna Full prescribing information. https://www.cerianna.com/wp-content/uploads/2020/05/cerianna-prescribing-information.pdf. Revised July 2020. Accessed May 27, 2020.

2 PETNET Solutions, Inc., and Zionexa USA. PETNET Solutions and Zionexa USA announce FDA approval of Cerianna (fluoroestradiol F-18). https://www.zionexa.com/wp-content/uploads/2020/05/press-release-zionexa-petnet-cerianna-fda-approval.pdf. Published May 27, 2020. Accessed May 28, 2020.

3 Gradishar W, Anderson BO, Abraham J, et al. NCCN Clinical practice guidelines in oncology. Breast cancer, version 5. 2020. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed May 27, 2020.

4 Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol*. 2020;38(12):1346-66. doi:10.1200/JCO.19.02309.

5 Blamey RW, Hornmark-Stenstam B, Ball G, et al. ONCOPOOL – A European database for 16,944 cases of breast cancer. *Eur J Cancer*. 2010;46(1):56-71. doi:10.1016/j.ejca.2009.09.009.

6 Cardoso F, Bartlett JMS, Slaets L, et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Ann Oncol*. 2018;29(2):405-417. doi:10.1093/annonc/mdx651.

7 Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985–2016. *The Breast*. 2017;31:46-50. doi:10.1016/j.breast.2016.10.005.

8 Aurilio D, Disalvatore G, Pruneri G, et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. *Eur J Cancer.* 2014;50(2):277-89. doi:10.1016/j.ejca.2013.10.004.

9 Chae SY, Ahn SH, Kim SB, et al. Diagnostic accuracy and safety of 16α-[^{18}F]fluoro-17β-oestradiol PET-CT for the assessment of oestrogen receptor status in recurrent or metastatic lesions in patients with breast cancer: a prospective cohort study. *Lancet Oncol*. 2019;20(4):546-55. doi:10.1016/S1470-2045(18)30936-7.

10 Peterson LM, Kurland BF, Schubert EK, et al. A phase 2 study of 16α-[^{18}F]-fluoro-17β-estradiol Positron Emission Tomography (FES-PET) as a Marker of Hormone Sensitivity in Metastatic Breast Cancer (MBC). *Mol Imaging Biol*. 2014;16:431-40. doi:10.1007/s11307-013-0699-7.

11 Kurland BF, Wiggins JR, Coche A, et al. Whole-Body Characterization of Estrogen Receptor Status in Metastatic Breast Cancer with 16α-18F-Fluoro-17β-Estradiol Positron Emission Tomography: Meta-Analysis and Recommendations for Integration into Clinical Applications. *Oncologist*. Published online May 6, 2020. doi:10.1634/theoncologist.2019-0967.

12 Boers J, Venema CM, de Vries EFJ, et al. Molecular imaging to identify patients with metastatic breast cancer who benefit from endocrine treatment combined with cyclin-dependent kinase inhibition. *Eur J Cancer*. 2020;126:11-20. doi:10.1016/j.ejca.2019.10.024.

13 Eisses B, Angus L, van der Vegt B, et al. Abstract PD4-09: Non-invasive estrogen receptor assessment by [^{18}F]-fluorestradiol (FES)-PET or circulating tumor cells predicts receptor status in patients with metastatic breast cancer. Abstract presented at: 2018 San Antonio Breast Cancer Symposium; December 4-8, 2018; San Antonio, TX. doi:10.1158/1538-7445.SABCS18-PD4-09.

14 Katzenellenbogen JA. The quest for improving the management of breast cancer by functional imaging: The discovery and development of 16α-[^{18}F]fluoroestradiol (FES), a PET radiotracer for the estrogen receptor, a historical review. *Nucl Med Biol*. Published online February 22, 2020. doi:10.1016/j.nucmedbio.2020.02.007.

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). (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 +1.844.946.6392 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

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: 07/2020

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
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

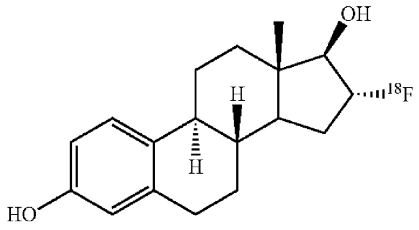
Risk Summary
There are no data on the presence of fluoroestradiol F 18 in human milk, or its effects on the breastfed infant or milk production. Lactation studies have not been conducted in animals. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration in order to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

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 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)]*.

Distributed by:
ZIONEXA US CORP.
10475 Crosspoint Blvd, Suite 250
Indianapolis, IN 46256