CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212155Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 22, 2020

To: Qi Feng, M.D.
Division of Medical Imaging Products (DMIP)

Sharon Thomas, Regulatory Project Manager, DMIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for CERIANNA™ (fluoroestradiol F 18) Injection, for intravenous use

NDA: 212155

In response to DMIP's consult request dated April 3, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Cerianna.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMIP on April 21, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 16, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
04/22/2020 04:33:52 PM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

To: Anthony Fotenos, MD, PhD
Clinical Reviewer, CDER/ORDPURM/DMIRM

From: Preeti Narayan, MD
Clinical Reviewer, CDER/OND/OHOP/DO1

Through: Christy Osgood, MD
Acting Clinical Team Leader Breast Oncology, CDER/OND/OHOP/DO1

Through: Laleh Amiri-Kordestani, MD
Associate Director, Division of Oncology 1 (DO1)

Date: March 24, 2020

Subject: DMIRM consult regarding NDA 212155 for a new F18-fluorestradiol (FES) PET agent.

References: Consult questions from DMIRM, proposed USPI, DMIRM sharepoint resources (midcycle), EDR

Background/Rationale:
Zionexa submitted NDA 212155 for F18-fluorestradiol (FES) under Section 5050(b)(2) of the Food, Drug and Cosmetic Act for the proposed indication of characterization of estrogen receptor status (b) (4) breast cancer.

FES is a radioactive agent for positron emission tomography (PET) imaging. FES has been noted to have affinity for the estrogen receptor. Development of FES for PET imaging allows for whole body imaging for estrogen receptors.

This NDA application included 15 studies and 3 meta-analyses that provide data in support of the indication claimed in this NDA. Among these, there are 6 clinical studies that address diagnostic accuracy, 6 older studies that did not use current clinical methodology and that provide supporting information, and 3 studies published only as a meeting abstract that, although insufficient to judge the quality of the research, do not disagree with the conclusions of the primary studies. One additional study included only ER-positive patients and thus did not

provide information on specificity. Per DMIRM efficacy review of these studies, there is adequate evidence FES-PET can detect ER expression on both primary and metastatic breast cancer.

A review of the safety date noted that the most common AEs generally are injection site pain and dysgeusia; however, data is limited as studies did not focus on AE incidence as FES agent was only administered once. Additionally, there is no information about the use of FES in pregnant women. Animal reproduction studies have not been conducted with FES.

Consultation Questions for CDER DO1:

1. **From the DO1 clinical perspective and in reference to National Comprehensive Cancer Network guidelines in patients with recurrent/Stage IV disease (or other applicable oncology guidance), please provide suggested edits, if any, with respect to the following DMIRM-recommended labeling revisions:**

   1 Indications and Usage
   Applicant
   FLUOROESTRADIOL F 18 is indicated for use with positron emission tomography (PET) imaging for characterization of estrogen receptor (ER) status (b) (4) breast cancer.

   DMIRM change to label:
   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.

   5 Warnings and Precautions
   Applicant
   (b) (4)

   DMIRM change to label:

   5.1 Risk of Misdiagnosis
   Inadequate Tumor Characterization and Other ER-Positive Pathology Breast cancer may be heterogeneous within patients and across time. CERIANNA targets neither human epidermal growth factor receptor 2 (HER2) nor the progesterone receptor (PR). The uptake of CERIANNA 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, ovaries,

prostate, and meninges. 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.

2.3 Assessment for Drug Interactions
Image patients with CERIANNA prior to starting systemic endocrine therapies that target ER (e.g., ER modulators, ER down-regulators, high-dose estrogen). In patients with concomitant use or a recent history of using these therapies, ensure an appropriate washout period prior to dosing with CERIANNA [see Drug Interactions (7.1)].

7.1 Systemic Endocrine Therapies that Target Estrogen Receptors
Certain classes of systemic endocrine therapies, including ER modulators, ER down-regulators, and high-dose estrogen, target ER and may reduce detection of ER-positive lesions after administration of CERIANNA. Table 2 provides estimated time periods over which ER binding may reduce fluoroestradiol F 18 binding following administration of ER-targeted systemic endocrine therapies (time 0 = date of last administered therapy).

Table 2. Approximate duration in weeks that therapy may reduce fluoroestradiol F 18 uptake

Therapy	**Duration**
ER modulator (e.g., tamoxifen, toremifene)	6 to 8 weeks
ER down-regulator (e.g., fulvestrant)	28 weeks
High-dose estrogen (e.g., ethinyl estradiol)	1 week

Image patients with CERIANNA prior to starting ER-targeted systemic endocrine therapies. In patients with concomitant use or a recent history of using these therapies, consider the washout period prior to dosing with CERIANNA [see Dosage and Administration (2.3)].

CDER DO1 Response:

Section 1: Indication

DMIRM proposed language:

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.

We recommend you add an additional sentence after the current indication statement similar to "Tissue biopsy must confirm that patients have ER-positive breast cancer disease per standard

IHC testing guidelines" to ensure patients are confirmed to have ER-positive disease and this PET imaging does not replace the standard practice of confirming recurrence of breast cancer by pathology.

It is not entirely clear to DO1 what the actual clinical benefit is for doing this PET imaging, given that patients will still require a biopsy to confirm ER-positive disease. DO1 recommends that you include the potential scenarios where patients may benefit from this PET imaging. These 3 scenarios include the following:

- When a IHC test is negative due to due heterogeneity in ER expression and by doing this PET imaging they can identify more ER+ patients.
- To detect ER positive lesion where biopsy is not feasible
- To prioritize lesion sub-sampling when biopsy of all lesions is not feasible

Section 5.1: Risk of Misdiagnosis

DMIRM proposed language:

> *Inadequate Tumor Characterization and Other ER-Positive Pathology Breast cancer may be heterogeneous within patients and across time. CERIANNA targets neither human epidermal growth factor receptor 2 (HER2) nor the progesterone receptor (PR). The uptake of CERIANNA 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, ovaries, prostate, and meninges. 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.*

DO1 recommends changing the heading "Risk of Misdiagnosis", as this implies this PET agent can be used for diagnosis of breast cancer. A tissue biopsy will still be required to confirm that a lesion is breast cancer and is ER-positive. DO1 agrees that this PET-imaging is not specific for ER-positive breast cancer and that a negative result does not exclude ER-positive metastatic disease. Given the risk of misdiagnosis and potential negative impact on a patient's survival, if an oncologist decides to use these test results for treatment decisions, and the fact this test should not replace the actual biopsy, the utility of this PET imaging is not clear to DO1 and it is unclear how the benefit/risk of this PET imaging is positive.

Oncologists generally order interval imaging to monitor a patients' response to therapy. Can this PET imaging be ordered in this scenario? If the utility of PET imaging has not been studied and should not be used in this setting, DO1 recommends you add a warning to the label regarding this.

Sections 2.3 and 7.1

DMIRM proposed language:

2.3 Assessment for Drug Interactions
Image patients with CERIANNA prior to starting systemic endocrine therapies that target ER (e.g., ER modulators, ER down-regulators, high-dose estrogen). In patients with concomitant use or a recent history of using these therapies, ensure an appropriate washout period prior to dosing with CERIANNA [see Drug Interactions (7.1)].

7.1 Systemic Endocrine Therapies that Target Estrogen Receptors
Certain classes of systemic endocrine therapies, including ER modulators, ER down-regulators, and high-dose estrogen, target ER and may reduce detection of ER-positive lesions after administration of CERIANNA. Table 2 provides estimated time periods over which ER binding may reduce fluoroestradiol F 18 binding following administration of ER-targeted systemic endocrine therapies (time 0 = date of last administered therapy).

Table 2. Approximate duration in weeks that therapy may reduce fluoroestradiol F 18 uptake

Therapy	**Duration**
ER modulator (e.g., tamoxifen, toremifene)	6 to 8 weeks
ER down-regulator (e.g., fulvestrant)	28 weeks
High-dose estrogen (e.g., ethinyl estradiol)	1 week

Image patients with CERIANNA prior to starting ER-targeted systemic endocrine therapies. In patients with concomitant use or a recent history of using these therapies, consider the washout period prior to dosing with CERIANNA [see Dosage and Administration (2.3)].

In general, DO1 agrees with the language proposed above for sections 2.3 and 7.1. Consider being clearer in the label and add a minimum wash-out period for each of these hormonal therapies to this label for clarity.

It is not clear what dose of estrogen (e.g., ethinyl estradiol) is considered “high dose”. DO1 recommends adding the exact dose that is considered high dose to the label. Fulvestrant is only approved for the treatment of advanced/metastatic breast cancer. If a patient is already started on fulvestrant, it is not clear why this PET imaging should be done (if it is done for an adjunct to biopsy to diagnose metastatic breast cancer.)

Patients with early stage breast cancer may receive adjuvant hormonal therapy for 5-10 years. If a patient is suspected to have a recurrence, normally a staging work-up is done that includes physical exam, lab tests, CT C/A/P and biopsy of the suspected metastatic lesion. Generally, this work up can be done quickly. However, if a patient is on tamoxifen and the oncologist needs to wait 8 weeks for washout, this makes the test not available to be an “adjunct” to the diagnosis of recurrent ER+ breast cancer.

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CHRISTY L OSGOOD
04/16/2020 10:22:52 AM

LALEH AMIRI KORDESTANI
04/16/2020 10:40:27 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 23, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 212155
Product Name and Strength:	Cerianna (fluoroestradiol F18) injection, 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL)
Applicant/Sponsor Name:	Zionexa
OSE RCM #:	2019-446-2
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 16, 2020 for Cerianna. We reviewed the revised container label and carton labeling for Cerianna (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Vee S. Label and Labeling Review for Cerianna (NDA 212155). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 21. RCM No.: 2019-446-1.

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/s/

SARAH K VEE
03/23/2020 10:50:07 AM

HINA S MEHTA
03/23/2020 05:16:23 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 21, 2020
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 212155
Product Name and Strength:	Fluoroestradiol F 18 injection, 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL)
Applicant/Sponsor Name:	Zionexa
OSE RCM #:	2019-446-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 17, 2020 for fluoroestradiol F 18. We reviewed the revised container label and carton labeling for fluoroestradiol F 18 (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label (vial label) and carton labeling (lead shield label) is unacceptable from a medication error perspective. We note the lack of the use of a comma for numbers greater than 1,000, placement of the strength, and the need to update the storage information. We provide recommendations for Zionexa below.

3 RECOMMENDATIONS FOR ZIONEXA

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (vial label and lead shield label)

[a] Vee S. Label and Labeling Review for fluoroestradiol F 18 (NDA 212155). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 21. RCM No.: 2019-446.

1. Consider stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000”.
2. We recommend moving the route of administration to below the strength. The strength should be listed first and then the route of administration below.

B. Lead shield label

1. Update the storage information to be consistent with the prescribing information so that the temperature in Fahrenheit is included. It should read “Store at 20°C to 25°C (68°F to 77°F)”.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 21, 2019
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 212155
Product Name and Strength:	Fluoroestradiol F-18 Injection, 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Zionexa
FDA Received Date:	February 27, 2019 and April 4, 2019
OSE RCM #:	2019-446
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Zionexa submitted an NME 505(b)(2) NDA for fluoroestradiol F-18 (NDA 212155). We reviewed the proposed prescribing information (PI), container label, and lead shield labeling for areas of vulnerability from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, container label, and lead shield labeling for fluoroestradiol F-18 for areas of vulnerability that may lead to medication errors. Our review of the proposed labeling identified several areas that can be improved to increase the prominence of important information. We provide recommendations for the Division in section 3.1 and the Applicant in section 3.2 to be implemented prior to approval of the NDA.

3.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information (PI)

1. To increase readability, a unit-of-measure should follow each numeric dose designation and the symbol '-' should be replaced with the word 'to'. Include, 'minutes', 'MBq', 'mCi', 'MBq/mL' and 'mCi/mL' after each numeric value pertaining to dosage and administration throughout the PI.
2. Add a space between the numerical value and unit of measure to increase readability and to avoid confusion. (b) (4) .

3. Consider stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".

B. Highlights of Prescribing Information

1. Place the recommended dose bullet as the first bullet in this section. (b) (4) [redacted]

2. Remove the last bullet in the section as the information is in Section 2 of the PI and does not seem to be needed in the highlights.

C. Full Prescribing Information

1. Section 2 Dosage and Administration

a. Delete the second and third sentences in the first paragraph of Section 2.2 as the information is already listed in the bullets right under the paragraph. Remove "[redacted] (b) (4)" as it is redundant.

b. The third bullet stated that Fluoroestradiol F18 can be diluted with 0.9% Sodium Chloride. However, the final volume of the diluted solution is not stated. If applicable, add the final volume the drug can be diluted to.

2. Section 16 Dosage Form and Strengths

a. Please include the NDC number under the how supplied section as currently it is missing.

3.2 RECOMMENDATIONS FOR ZIONEXA

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The approved route of administration, "For Intravenous Use Only" is currently embedded among other information and therefore may be easily missed. Please move to directly below the product strength and bold to make it more prominent.

2. If space permits, per 21 CFR 201.55, include the "Usual dosage: See prescribing information" statement.

3. To increase readability, a unit-of-measure should follow each numeric dose designation and the '-' should be replaced with the word 'to'. Include, 'MBq/mL' and 'mCi/mL' after each numeric value pertaining to dosage and administration throughout the PI.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fluoroestradioal F-18 received on April 5, 2019 from Zionexa.

Table 2. Relevant Product Information for Fluoroestradioal F-18	
Initial Approval Date	N/A
Active Ingredient	Fluoroestradiol F-18
Indication	Indicated for use with positron emission tomography (PET imaging) for characterization of estrogen receptor (ER) status (b) (4) (b) (4) breast cancer
Route of Administration	Intravenous injection
Dosage Form	Injection
Strength	148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL)
Dose and Frequency	(b) (4)
How Supplied	50 mL multiple-dose glass vial
Storage	Store at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Store within the original container in radiation shielding.
Container Closure	(b) (4) glass, gray (b) (4) rubber stopper, and aluminum crimp seal

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Fluoroestradioal F-18 labels and labeling submitted by Zionexa.

- Container label received on February 27, 2019
- Lead shield labeling received on February 27, 2019
- Prescribing Information (Image not shown) received on April 5, 2019

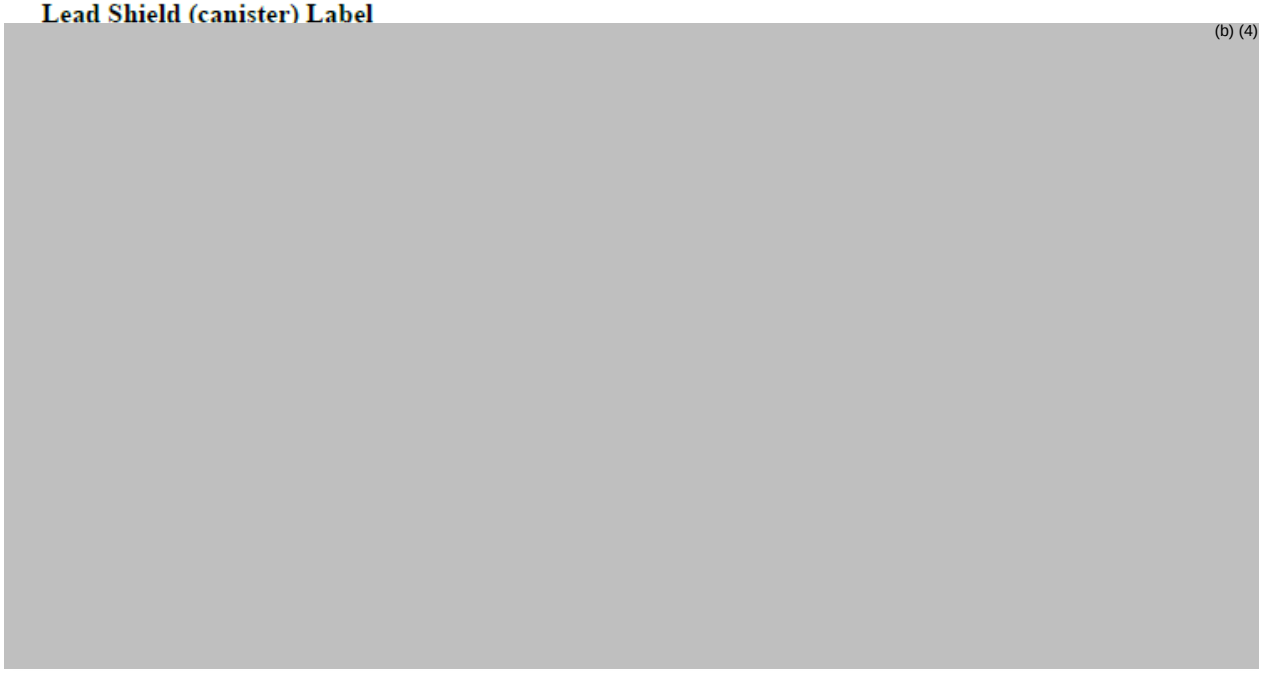
B.2 Label and Labeling Images

Vial (immediate container Label)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Lead Shield (canister) Label

(b) (4)



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