CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214032Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	December 16, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214032
Product Name and Strength:	Illuccix (kit for the preparation of gallium Ga 68 gozetotide) for injection, 25 mcg/vial
Applicant/Sponsor Name:	Telix Pharmaceuticals
OSE RCM #:	2020-2022-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Tellix Pharmaceuticals submitted revised Illuccix vial 1 container label, carton labeling configuration A, carton labeling configuration B, buffer A container label, buffer B container label, diagnostic label, and syringe label received on December 15, 2021 for Illuccix (kit for the preparation of gallium Ga 68 gozetotide injection) under NDA 214032. We reviewed the revised Illuccix vial 1 container label, carton labeling configuration A, carton labeling configuration B, buffer A container label, buffer B container label, diagnostic label, and syringe label for Illuccix (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations made during a previous labeling review and via email on December 8, 2021 and December 13, 2021.[a]

2 CONCLUSION

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

[a] Kane, D. Label and Labeling Review for Illuccix (NDA 214032). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 APR 06. RCM No.: 2020-2022.

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/s/

DEVIN R KANE
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HINA S MEHTA
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: November 24, 2021

To: Shane Masters, M.D.
Division of Imaging and Radiation Medicine (DIRM)

Diane Hanner, Regulatory Project Manager, DIRM

Younsook Kim, Associate Director for Labeling, DIRM

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ILLUCCIX (kit for the preparation of gallium Ga 68 gozetotide injection), for intravenous use

NDA: 214032

In response to DIRM's consult request dated November 22, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Illuccix.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DIRM on November 22, 2021, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DIRM on November 23, 2021, 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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DAVID F FOSS
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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:	April 6, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 214032
Product Name, Dosage Form, and Strength:	Illuccix (kit for the preparation of Ga 68 PSMA-11) for injection, 25 mcg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Telix Pharmaceuticals
FDA Received Date:	September 23, 2020
OSE RCM #:	2020-2022
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Telix Pharmaceuticals submitted NDA 214032 Illuccix (kit for the preparation of Ga 68 PSMA-11) for injection on September 23, 2020. Illuccix, after radiolabeling with Ga-68, is a radioactive diagnostic agent [redacted] We evaluated the proposed Illuccix prescribing information (PI), vial container label, carton labeling configuration A, carton labeling configuration B, buffer A vial container label, buffer B vial container label, [redacted] label, diagnostic label, and syringe label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

On July 24, 2019, a pre-NDA meeting was held with Telix Pharmaceuticals. During this meeting the Agency recommended that the Sponsor submit a comprehensive risk analysis for the proposed product.[a] On April 24, 2021, Telix Pharmaceuticals submitted a proactive risk assessment and comparative analysis for Ga 68 PSMA-11 under IND 144421. DMEPA evaluated the proactive risk assessment and comparative analysis. The review concluded that results from a human factors validation study do not need to be submitted for Agency's review as part of the marketing application for Ga 68 PSMA-11.[b]

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	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

[a] Memorandum of Meeting Minutes for Ga-68 PSMA 11 (IND 144421). Silver Spring (MD): FDA, CDER, ODEIV/DMIRM (US); 2019 AUG 21.

[b] Kane, D. Ga-68 PSMA 11 (IND 144421) Proactive Risk Assessment and Comparative Analysis Review. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 02. RCM No. 2020-855.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

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

Telix Pharmaceuticals submitted a 505(b)(2) application to obtain marketing approval of Illuccix for injection.

We note Illuccix will be supplied in two different kit configurations, configuration A and configuration B. We note configuration A differs from configuration B based on the buffer supplied in the kit. Both buffer A and buffer B contain 150 mg of sodium acetate, however, in addition to the sodium acetate, buffer A also contains 0.292 M HCl solution in 2.5 mL whereas buffer B contains 0.175 M HCl solution in 6.4 mL. The determination of which kit configuration to be used is based on the radiopharmacy's source of gallium Ga 68. Kit for the preparation of Illuccix configuration A will be for use with Eckert and Ziegler GalliaPharma Ge-68/Ga-68 generator and for cyclotron produced Ga-68 with GE FASTlab. Kit for the preparation of Illuccix configuration B will be for use with IRE ELIT Galli Eo Ge-68/Ga-68 generator. We note the kit configurations differ based on the buffer that is supplied and the two configurations will contain the equal amounts of 25 mcg PSMA-11 active ingredient vials. Additionally, we note Telix Pharmaceuticals proposes prominently displaying "A" or "B" on the carton labeling to differentiate the two configuration types and defining the appropriate use of that kit configuration underneath the letter.

We performed a risk assessment of the for the proposed prescribing information (PI), vial container label, carton labeling configuration A, carton labeling configuration B, buffer A vial container label, buffer B vial container label, (b) (4) label, diagnostic label, and syringe label Illuccix to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI, vial container label, carton labeling configuration A, carton labeling configuration B, buffer A vial container label, buffer B vial container label, (b) (4) label, diagnostic label, and syringe label for Illuccix identified areas of vulnerability that may lead to medication errors. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Illuccix prescribing information (PI), vial container label, carton labeling configuration A, carton labeling configuration B, buffer A vial container label, buffer B vial container label, (b) (4) label, diagnostic label, and syringe label identified areas of vulnerability that may lead to medication errors. Below, we have provided

recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Telix Pharmaceuticals so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. As currently presented, we note that the recommended dose statement contains an inappropriate abbreviation and needs clarity. Revise to read "Recommended dosage is (b) (4) MBq ((b) (4) mCi) as a bolus intravenous injection (2.3)."

b. The last bullet of the Highlights Dosage and Administration section contains information (b) (4) We note this information is not required to be in the highlights, thus we recommend removing this information.

c. We recommend having the last bullet of this section read "See Full Prescribing Information for preparation, administration, imaging, and radiation dosimetry information."

2. Dosage Forms and Strengths

a. We recommend revising information as part of vial 1 for consistency with the other sections. Revise to "Vial 1 contains 25 mcg PSMA-11 and 10 mcg D-mannose as a lyophilized powder (stabilizer)".

b. We note underneath 'Vial 2' the buffer is defined as configuration A or configuration B. We recommend revising this information for clarity to read "Vial 2A in Kit Configuration A (for use with....)" and "Vial 2B in Kit Configuration B (for use with...)".

c. As currently presented, 'Vial 3' is defined as a (b) (4) We recommend revising this statement read "(Empty (b) (4) (b) (4) l) for the collection of Ga-68".

d. This Section defines the strength of Illuccix as "up to 247 MBq (6.7 mCi) per mL. Each vial would contain up to 1850 MBq (50 mCi)." We recommend providing the strength as a range with both the lowest potential strength and the highest potential strength presented.

B. Prescribing Information

1. Section 2: Dosage and Administration

a. We note not all numeric values are followed by the appropriate units in Section 2. We recommend including the appropriate units after each numeric value.

b. As currently presented, Section (b) (4) contains information (b) (4) and Section (b) (4) contains information (b) (4) We recommend making the recommended dosage and administration instructions Section 2.2 and making the patient preparation information Section 2.3.

c. The second line of the current Section (b) (4) states (b) (4) We note that the preparation of Illuccix requires the Ga-68 chloride eluate as well as the addition of the appropriate buffer solution prior to patient administration. We recommend revising this statement to read "After addition of the appropriate buffer and reconstitution with Ga-68 chloride eluate from an appropriate source...".

d. We note the second paragraph of Section (b) (4) Recommended Dosage and Administration Instructions contains the statement (b) (4) We recommend including the appropriate sources of Ga 68 eluate in Section (b) (4)

e. As currently presented, the first line of Section 2.4 states "Illuccix is supplied as (b) (4)". We recommend revising this statement to read "Illuccix is supplied as 3 vials in 2 different configurations which allows for direct preparation of Ga 68 PSMA-11 with eluate from one of the following...".

f. As currently presented, step e of Section 2.4 under preparation states to (b) (4) We recommend revising this step to read, "Remove the vial cap from all three vials".

g. We note step 'g' under Prepare Ga 68 PSMA-11 states to use the shortest possible needle, and to use a needle that is dilute acid resistant. We recommend stating the specific type of needle used for gallium transfer (i.e. (b) (4) needles).

h. As currently presented, step 'h' under Prepare Ga 68 PSMA-11 provides important information regarding the type of syringe to use. We recommend revising step h to read "Use only plastic syringes for preparation and administration. Do not use syringes with rubber plungers.".

i. We note in step 4 under Reconstitution with Eckert and Ziegler GalliaPharm Generator as well as in step 2 of the radiosynthesis procedure contain numeric values that are immediately followed by their

units without a space between the value and the units. We recommend including a space between all numeric values and their units in order to avoid confusion. Revise "5mL" to "5 mL".

j. We note Step (b) (4) underneath Radiosynthesis Procedure in Section 2.4 instructs the end user to (b) (4) We recommend provided the approved storage temperature range along with the "ambient room temperature" phrase for clarity.

k. We recommend revising Section (b) (4) to bullet points for ease of readability and so that important information is not missed.

l. We note the presence of trailing zeros in Section (b) (4) Radiation Dosimetry and in Table 2: Estimated Radiation Absorbed (b) (4) We recommend removing the use of trailing zeros throughout Section (b) (4) and Table 2 in order to avoid a ten-fold misinterpretation of the presented value.

2. Section 3: Dosage Forms and Strengths

a. We recommend revising information as part of vial 1 for consistency with the other sections. Revise to "25 mcg PSMA-11 and 10 mcg D-mannose as a lyophilized powder (stabilizer)".

b. The second line of Section 3 states (b) (4) (b) (4) We recommend deleting this statement as it is not needed.

c. We note the contents of 'Vial 2' will differ based on the source of Ga-68, and the buffer supplied in kit configuration A is different from the buffer supplied in kit configuration B. We recommend revising the information on 'Vial 2' to read "150 mg sodium acetate in HCl buffer (supplied as 2A or 2B, depending on Ga-68 source).".

d. The last line of Section 3 states (b) (4) We recommend revising the strength to include a range with both the lower value of the strength range and the upper value.

3. Section 16: How Supplied/Storage and Handling

a. We note the first line of Section (b) (4) 2 states (b) (4) (b) (4) We recommend revising this statement to include the phrase 'kit for the preparation of…', and revising the storage temperature requirements to include the Fahrenheit equivalent values in paranthesis and replacing the use of the symbol '-' with its intended

meaning 'to'. Revise the first line to read "Store refrigerated upright in original packaging at 2° to 8°C (36° to 46°F). Do not freeze.".

b. We note Section 16.2 states that after reconstitution and radiolabeling Illuccix is to be stored in appropriate radiation shielding (b) (4) (b) (4) We recommend including the approved room temperature range for clarity.

c. As currently presented, Section 16 states Illuccix is a (b) (4) whereas Section 3 states it is a "multiple-dose kit". We recommend consistency throughout the PI for the package type and referring to the package type as "multiple-dose kit".

4.2 RECOMMENDATIONS FOR TELIX PHARMACEUTICALS

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

A. PSMA-11 Container Label

1. As currently presented, the label states "Vial 1 (b) (4)". We recommend revising this statement to better define the vial contents. Revise to read "Vial 1 (Stabilizer vial with lyophilized powder)".
2. We note the proposed container label states (b) (4) (b) (4) We recommend revising this statement to read "Recommended Dosage: See Prescribing Information".
3. As currently presented, the storage temperature requirements are only provided in degrees Celsius. Additionally, we note the use of the symbol '-' when presenting the storage temperature range to represent the word 'to'. We recommend revising the storage temperature statement to read "Store refrigerated upright in original packaging at 2° to 8°C (36° to 46°F). Do not Freeze".
4. We note the manufacturer's name is absent from the proposed PSMA-11 container label. We recommend including the manufacturer's name on the label.

B. Carton Labeling (Configuration A and Configuration B)

1. We note the presence of the graphic on the proposed carton labeling displayed (b) (4) As currently presented it may interfere with the readability (b) (4) We recommend moving the graphic to another location on the label or decreasing the size of the graphic so that (b) (4)
2. We note there are two different configurations of packaging for Illuccix, Configuration A and Configuration B based on the source of gallium Ga 68. We recommend increasing the prominence for the "For Use With..." statements on both the proposed Configuration A and Configuration B carton labeling to make the source of gallium Ga 68 more prominent to prevent confusion.

3. As currently presented, the storage temperature requirements are only provided in degrees Celsius. Additionally, we note the use of the symbol '-' when presenting the storage temperature range to represent the word 'to'. We recommend revising the storage temperature statement to read "Store refrigerated upright in original packaging at 2° to 8°C (36° to 46°F). Do not Freeze".
4. The carton labeling states to store the radiolabeled Ga 68 PSMA-11 at (b) (4) (b) (4) We recommend including the approved room temperature range, in both degrees Celsius and degrees Fahrenheit, in order to prevent confusion.
5. We note the statement (b) (4) (b) (4) We recommend revising this statement to read "See Prescribing Information for preparation and administration instructions".
6. We note the carton labeling contains a placeholder for the expiration date and does not contain the proposed format for the expiration date. We recommend that the expiration date appears in YYYY-MM-DD format is only numerical characters are used or in YYYY-MMM-DD is alphabetical characters are used to represent the month.
7. As currently presented, the principle display panel of the carton labeling states (b) (4) We recommend revising this statement to read "Multiple-Dose Kit" in order to clearly define the container type and align with the prescribing information.

C. Buffer Container Label (Buffer A and Buffer B)
1. As currently presented, the storage temperature requirements are only provided in degrees Celsius. Additionally, we note the use of the symbol '-' when presenting the storage temperature range to represent the word 'to'. We recommend revising the storage temperature statement to read "Store refrigerated upright in original packaging at 2° to 8°C (36° to 46°F). Do not Freeze".
2. We note the statement (b) (4) (b) (4) We recommend revising this statement to read "See Prescribing Information for preparation and administration instructions".
3. As currently presented, the proposed container label for both Buffer A and Buffer B state they contain (b) (4) Additionally, we note that Buffer A differs from Buffer B. We recommend providing the specific buffer contents on both the Buffer A container label and Buffer B container label.

D. (b) (4) Label
1. We note the proposed label defines this component as a (b) (4) However, we note the prescribing information refers to this vial as the (b) (4) (b) (4) We recommend revising the language on the label to align with the language used in the prescribing information. Revise to read "Empty (b) (4) (b) (4)".

E. Diagnostic Label

1. We note the proposed label states [redacted] We recommend revising this statement to read “See Prescribing Information for dosage and administration instructions”.
2. The storage requirements on the proposed diagnostic label state [redacted] We recommend including the approved room temperature range, in both degrees Celsius and degrees Fahrenheit, in order to prevent any confusion.
3. We note the placeholder line for [redacted] We recommend revising this line to read “Discard After: _____Time _____Date”.
4. We note the placeholder line for “EOS”. Since “EOS” is not defined elsewhere on the label, we recommend spelling out “End of Synthesis”. We recommend revising this line to read “End of Synthesis: _____ Time _____Date”.
5. As currently presented, the “Rx Only” statement [redacted] We recommend presenting the “Rx Only” statement on its own line [redacted]

F. Syringe Label

1. We note that Illuccix must be used within 4 hours of reconstitution. We recommend including this information on the syringe label. Revise the syringe label to include the statement “Do not use and discard 4 hours after reconstitution”.
2. As currently presented, the “Rx Only” statement [redacted] We recommend presenting the “Rx Only” statement on its own line [redacted]

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Illuccix received on September 23, 2020 from Telix Pharmaceuticals.

Table 2. Relevant Product Information for Illuccix	
Initial Approval Date	N/A
Active Ingredient	kit for the preparation of Ga 68 PSMA-11
Indication	(b) (4)
Route of Administration	Intravenous
Dosage Form	for injection
Strength	25 mcg/vial
Dose and Frequency	(b) (4) intravenous dose of (b) (4) MBq (mCi), with a range of (b) (4) MBq (to mCi) and (b) (4) 25 mcg of PSMA-11.
How Supplied	(b) (4)

	(b) (4)
Storage	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 7, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Ga 68 PSMA-11. Our search identified 1 previous reviews[c], and we considered our previous recommendations to see if they are applicable for this current review.

Table 1. Summary of Previous DMEPA Reviews for Illuccix

OSE RCM #	Review Date	Summary of Recommendations
2020-855	July 7, 2020	Our review of the proactive risk assessment did not identify any critical tasks that are not already mitigated by the Telix's proposed packaging and labeling proposal. In the instance that the wrong buffer configuration is ordered and used with the incorrect source of gallium, we note that the resulting solution would not pass radiochemical purity testing and thus, would not be administered to the patient. We note that any residual risks involved in using the wrong buffer can be mitigated through additional labels and labeling interventions during the review cycle and the acceptability of the labels and labeling (to ensure adequate packaging differentiation) is a review issue. Thus, we agree with Telix's mitigation strategies and justification for not submitting the results from a human factors (HF) validation study with the future marketing application to support the proposed product.

[c] Kane, D. Proactive Risk Assessment and Comparative Analysis Review for Ga 68 PSMA-11 (IND 144421). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 07. RCM No.: 2020-855.

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Illuccix labels and labeling submitted by Telix Pharmaceuticals.

- (b) (4) Container Label received on September 23, 2020
- Carton Labeling Configuration A received on September 23, 2020
- Carton Labeling Configuration B received on September 23, 2020
- Buffer A Vial Container Label received on September 23, 2020
- Buffer B Vial Container Label received on September 23, 2020
- (b) (4) Label received on September 23, 2020
- Diagnostic Label received on September 23, 2020
- Syringe Label received on September 23, 2020
- Prescribing Information (Image not shown) received on September 23, 2020, available from \\CDSESUB1\evsprod\nda214032\0000\m1\us\draft-labeling-text.docx

G.2Label and Labeling Images

(b) (4)

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

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