CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216820Orig1s000

OTHER REVIEW(S)

Division of Imaging and Radiation Medicine

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 216820

Name of Drug: Kit for the Preparation of Technetium Tc 99m Mertiatide Injection

Applicant: Jubilant DraxImage Inc., dba Jubilant Radiopharma

Labeling Reviewed

Submission Date: March 30, 2022; May 3, 2022; December 13, 23, 2022; January 5, 2023

Receipt Date: March 30, 2022; May 3, 2022; December 13, 23, 2022; January 5, 2023

Background and Summary Description:

Jubilant DraxImage Inc. dba Jubilant Radiopharma, Applicant of NDA 216820 Kit for the Preparation of Technetium Tc 99m Mertiatide Injection, requested a meeting on October 15, 2021, to confirm the following with the Agency:

- That the Application can be submitted as a 505(b)(2)
- That the Application can rely on Technescan MAG3™ from Curium, NDA 019882, as the RLD for evidence of safety and efficacy derived from nonclinical, clinical, and postmarketing findings
- That *in vivo* bioavailability or bioequivalence of JDI's proposed product with the RLD is self-evident and hence, a bio-waiver based on the FDA 21CFR 320.22(b)(ii) requirement will be granted to their Application.

An advice letter containing the FDA responses to the meeting request and Sponsor's submission of January 12, 2022, (meeting request cancelled on December 15, 2022) was sent to the Sponsor on February 15, 2022.

The Applicant in response submitted this application on March 30, 2022.

NDA 216820, Kit for the Preparation of Technetium Tc 99m Mertiatide Injection is indicated for the diagnosis of congenital and acquired renal abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients aged 30 days and older. It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex.

The Application has a Standard Review with a PDUFA due date of January 30, 2023, reviewed under the 505(b)(2) regulatory pathway.

Review

The labeling was reviewed by the following:

CMC: ATL: Ravindra Kasliwal/Danae Christodoulou

- Drug Product: Ravindra Kasliwal/Danae Christodoulou
- Drug Substance: Joseph Leginus/Sithamalli Chandramouli
- Biopharmaceutical: Nadia Ahmed/Om Anand
- Process/Facility: Andrew Idzior/ Sateesh Sathigari
- Microbiology: David Bateman/ Laura Wasil

Clinical: Shane Masters, Reviewer/TL

Biostatistics: Jyoti Zalkikar, Reviewer/Sue-Jane Wang, Ag. Director

Clinical Pharmacology: Sriram Subramaniam, Reviewer /Christy John, TL

Nonclinical: Olayinka Dina, Reviewer/Jonathan Cohen, Ag. TL

Labeling: Younsook Kim, Associate Director of Labeling (ADL)

DPMH -Pediatric: Christos Mastroyannis, Reviewer/ Tamara Johnson, TL

OPDP: David Foss, Reviewer/James Dvorsky, TL

OSE DMEPA: Devin Kane, Reviewer/Hina Mehta, TL

All the reviews are archived in DARRTS and in Panorama for CMC reviews. Labeling review activities were overseen by the Associate Director of Labeling, Younsook Kim.

The Applicant's response to the Agency's IR of April 5, 2022, to convert their Prescribing Information to PLR/PLLR format was received on May 3, 2022.

The labeling comments of prescribing information, container, and carton were first communicated to the Applicant on December 2, 2022, and the Applicant's responses with their revisions were received on December 13, 2022. Additional Carton and Container revisions were sent to the Applicant on December 22, 2022, and a prompt response was received from the Applicant on December 23, 2022. Further revisions to the Prescribing Information and Carton and Container labels were sent to the Applicant on January 4, 2023, and the Applicant responded with further comments January 5, 2023.

Recommendations

The submitted draft labeling, identified as NDA 216820 labeling/Prescribing Information, specifically, the label submitted on May 3, 2022, was recommended for approval after the acceptance of the Agency's and Applicant's revisions as finally submitted by the Applicant on January 5, 2023.

The entire Prescribing Information is included showing the revisions. The attached Prescribing Information is the agreed upon labeling between FDA and the Applicant.

Modupe Fagbami

Regulatory Project Manager Date

Shane Masters, M.D., Ph.D.

Lead Clinical Reviewer Date

Younsook Kim. Pharm.D., Ph.D.

Associate Director, Labeling Date

Kyong (Kaye) Kang, Pharm D.

Chief, Project Management Staff Date

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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YOUNSOOK C KIM
01/26/2023 02:56:42 PM

KYONG A KANG
01/26/2023 03:14:35 PM

ADL Review of Prescribing Information
(Division of Imaging and Radiation Medicine)

Product Title	**KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m MERTIATIDE injection, for intravenous use**
Applicant	Jubilant Draximage Inc.
Application/Supplement Number	NDA 216820/Original
Type of Application/Submission[1]	505(b)(2) New Drug Application (NDA)
Is Proposed Labeling in "Old" Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	Y
Is Labeling Being Converted to PLLR? (Y/N)	Y
Proposed Indication(s) (if applicable)	Technetium Tc 99m Mertiatide is a renal imaging agent for use in the diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients. It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex.
Approved Indication(s)	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection, after radiolabeling with technetium-99m, is a radioactive diagnostic agent indicated for use in the diagnosis of congenital and acquired renal abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients. It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex.
Date FDA Received Application	March 29, 2022
Review Classification (Priority/Standard)	Standard
Action Goal Date	January 30, 2023
Review Date	January 6, 2023
Reviewer	Younsook Kim, Pharm. D., Ph.D.

SUBMISSION BACKGROUND

The applicant is seeking marketing approval of kit for the preparation of technetium Tc 99m mertiatide injection for use in the diagnosis of certain urinary tract abnormalities relying on FDA's previous findings of the safety and effectiveness of technetium Tc 99m mertiatide for NDA 019882, TECHNESCAN MAG3 by Curium approved in 1990. The listed drug (LD) is currently marketed and the last approved labeling, S-002 dated 02/26/1993, is in non-PLR format.

[1] Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

The proposed labeling was consistent with the LD labeling except that the format is in PLR/PLLR to comply with the Pregnancy and Lactation Labeling Rule published in the Federal Register in December 2014 [*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, 79 FR 233, December 4, 2014, see 21 CFR 201.56(a and d) and 201.57 (c)(9)(i, ii, and iii)].

This review includes a high-level summary of the rationale for major changes to the PI as compared with the applicant's draft PI (see the table below).

Full Prescribing Information Sections[1]	**Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)**[2]

1 INDICATIONS AND USAGE	• (b) (4) [redacted] The age group of pediatric patients "aged 30 days and older" was added based on the pediatric use statement in the LD labeling: "Safety and effectiveness in pediatric patients under the age of 30 days have not been established."
	• Naming drug products in radiopharmaceutical kit labeling is different. In general, the INDICATIONS AND USAGE section uses the proprietary or nonproprietary name of the drug product distributed by a manufacturer (e.g., kit for the preparation of technetium Tc 99m mertiatide injection) whereas the DOSAGE AND ADMINISTRATION section uses the nonproprietary name of the finished product (e.g., technetium Tc 99m mertiatide injection). To make a transition between the two different drug names, the Division has implemented the following phrases for radiopharmaceutical kit labeling:
	  o A phrase "after radiolabeling with *{name of radionuclide}*" immediately after the product name in the INDICATIONS AND USAGE section
	  o A phrase "After radiolabeling, *{name of the product used in the indication statement}* produces *{name of the finished product}*" in the beginning of the DOSAGE AND ADMINISTRATION section.

2 DOSAGE AND ADMINISTRATION	• Radiation safety language to minimize radiation exposure was added as class labeling for radiopharmaceutical drugs:
	  o Drug handling
	  o Patient hydration before and after the drug administration.
	• Subheadings for patient population (e.g., Adults) and route of administration were added to the Recommended Dosage subsection for clarity.
	• The Drug Preparation subsection was edited to present the information in a clear, concise manner, using active voice and command language and in the same order as healthcare practitioners use the information.
	• Radiation dosimetry table was reformatted for consistency with

	other recently approved radiopharmaceutical drugs: o Radiation doses were presented per injected activity (i.e., mSv/MBq) o [redacted] (b) (4) o Age groups were reordered from adults to pediatric patients by decreasing age • The data for 8 days old was retained in the radiation dosimetry table even though the drug product is not indicated for patients younger than 30 days old because the 8 day old data will be useful for healthcare practitioners to estimate the radiation dose for patients between 30 days to 1 year old. A statement "Technetium Tc 99m Mertiatide Injection is not approved for pediatric patients younger than 30 days old *[see Indications and Usage (1)]*" was added to the table not to imply any unapproved use per 21 CFR 201.57(c)(2)(iv).
4 CONTRAINDICATIONS	This section states "None".
5 WARNINGS AND PRECAUTIONS	• Radiation risk was added as class labeling for radiopharmaceutical drugs. • The proposed languages by the applicant were either deleted due to redundancy or relocated to more appropriate sections such as the DOSAGE AND ADMINISTRATION section.
6 ADVERSE REACTIONS	[redacted] (b) (4) was revised to "elevation in blood pressure" for accuracy.
7 DRUG INTERACTIONS	This section was omitted.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	• 8.1 Pregnancy and 8.2 Lactation: These subsections were revised per the DPMH recommendations (see DARRTS). • 8.4 Pediatric Use: Pediatric use statements were added to indicate that the drug product is approved for pediatric patients aged 30 days and older but not for younger than 30 days based on the approved indications and the Pediatric Use statement of the listed drug (LD). The basis of approval for the indicated pediatric population required by 21 CFR 201.57(c)(9)(iv)(D) was omitted due to lack of information in the LD labeling. • 8.5 Geriatric Use: The proposed geriatric use statement was an alternative statement for one of the [redacted] (b) (4) The proposed statement was further revised due to lack of information about clinical experience in geriatric patients and inapplicability of recommending at the low end of the dosing range for radiopharmaceutical drugs.
10 OVERDOSAGE	General instructions to minimize radiation exposures in case of overdose were added such as hydration and diuretic use.

12 CLINICAL PHARMACOLOGY	• The proposed text was rearranged to appropriate subsections: 12.1 Mechanism of Action, 12.2 Pharmacodynamics, and 12.3 Pharmacokinetics. • Redundant terms (e.g., "[redacted] (b) (4)" after "healthy subjects") or ambiguous terms (e.g., [redacted] (b) (4)) were omitted.
13 NONCLINICAL TOXICOLOGY	No changes were made.
14 CLINICAL STUDIES	This section was omitted due to lack of information in the LD labeling.
17 PATIENT COUNSELING INFORMATION	Adequate hydration, pregnancy and lactation were added for healthcare practitioners to discuss with their patients.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Refer to Quality Integrated Review for sections 2.4 Drug Preparation, 3, 11, and 16.

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the (FOR NDAs/BLAs: applicant's draft PI (FOR EFFICACY SUPPLEMENTS: currently approved PI and the applicant's draft PI).

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/s/

YOUNSOOK C KIM
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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:	January 6, 2023
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216820
Product Name and Strength:	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection, 1 mg betiatide per vial
Applicant/Sponsor Name:	Jubilant DraxImage Inc., dba Jubilant Radiopharma (Jubilant)
OSE RCM #:	2022-1357-2
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Jubilant DraxImage Inc., dba Jubilant Radiopharma (Jubilant) submitted revised diagnostic radioassay labels on December 23, 2022 and revised vial container label and carton labeling on January 5, 2022 for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection under NDA 216820. We reviewed the revised vial container label, carton labeling, and diagnostic radioassay label for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and in response to recommendations from the Office of Pharmaceutical Quality (OPQ).

2 CONCLUSION

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

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[a] Kane, D. Label and Labeling Review for Kit for the Preparation of Technetium Tc 99m Mertiatide (NDA 216820). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 DEC 15. RCM No.: 2022-1357-1.

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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: December 21, 2022

To: Modupe Fagbami, Regulatory Project Manager, Division of Imaging and Radiation Medicine (DIRM)

Shane Masters, Clinical Reviewer, 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 KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m MERTIATIDE injection, for intravenous use

NDA: 216820

Background:

In response to DIRM's consult request dated June 2, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m MERTIATIDE injection, for intravenous use.

PI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 19, 2022, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on December 13, 2022, and we do not have any comments at this time.

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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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 15, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216820
Product Name and Strength:	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection, 1 mg betiatide per vial
Applicant/Sponsor Name:	Jubilant DraxImage Inc., dba Jubilant Radiopharma (Jubilant)
TTT ID #:	2022-1357-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Jubilant DraxImage Inc., dba Jubilant Radiopharma (Jubilant) submitted revised vial container label, carton labeling, and diagnostic radioassay label on December 13, 2022 for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection under NDA 216820. We reviewed the revised vial container label, carton labeling, and diagnostic radioassay label for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection (Appendix A) to determine if they are 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 vial container label, carton labeling and diagnostic radioassay label are unacceptable from a medication error perspective. We recommend revising the storage information statements in order to align with the information in the Prescribing Information. We provide our recommendations below.

[a] Kane, D. Label and Labeling Review for Kit for the Preparation of Technetium Tc 99m Mertiatide (NDA 216820). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 NOV 28. TTT ID No.: 2022-1357.

3 RECOMMENDATIONS FOR JUBILANT DRAXIMAGE INC., DBA JUBILANT RADIOPHARMA

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

A. Vial Container Label

1. We note the proposed vial container label includes the statement "(b) (4) (b) (4)". We recommend revising this statement to read "Use within 6 hours of radiolabeling" to align with the information presented in the prescribing information.

B. Carton Labeling

1. We note the proposed carton labeling includes the statement "(b) (4) (b) (4)". We recommend revising this statement to read "Use within 6 hours of radiolabeling" to align with the information presented in the PI.

C. Diagnostic Radioassay Label

1. As currently presented, the storage information statement presented on the proposed diagnostic radioassay label lacks information regarding proper shielding for the radiolabeled product. Additionally, the storage information differs from the information presented in the PI. We recommend revising the storage information statement on the proposed diagnostic radioassay label to read "Store vial upright in shielding to protect from radiation at room temperature 15°C to 30°C (59°F to 86°F). Use within 6 hours of radiolabeling.".

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LABEL AND LABELING REVIEW
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)

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

Date of This Review:	November 28, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216820
Product Name, Dosage Form, and Strength:	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection, 1 mg betiatide per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Jubilant DraxImage Inc., dba Jubilant Radiopharma (Jubilant)
FDA Received Date:	March 30, 2022 and May 3, 2022
OSE TTT #:	2022-1357
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Jubilant DraxImage Inc., dba Jubilant Radiopharma submitted a 505(b)(2) application for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection, on March 30, 2022. Kit for the Preparation of Technetium Tc 99m Mertiatide Injection is a renal imaging agent proposed for use in the diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients. It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex. We evaluated the proposed Kit for the Preparation of Technetium Tc 99m Mertiatide Injection prescribing information (PI), vial container label, carton labeling, and diagnostic radioassay label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

Kit for the Preparation of Technetium Tc 99m Mertiatide Injection (NDA 216820) relies upon the reference listed drug, Technescan MAG3 (kit for the preparation of technetium Tc 99m Mertiatide) under NDA 019882. Technescan MAG3 is currently marketed in multiple-dose vials containing 1 mg betiatide per vial as a lyophilized powder. The proposed product will be available in the same presentation as the reference product.

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 – N/A
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

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 note the proposed Kit for the Preparation of Technetium Tc 99m Mertiatide Injection product has the same active ingredient, strength (1 mg betiatide per vial) in multiple-dose vials, dosage form (injection), route of administration (intravenous), recommended dose (185 MBq (5 mCi) to 370 MBq (10 mCi) for adult patients, and 2.6 MBq/kg (70 microCi/kg) to 5.2 MBq/kg (140 microCi/kg) with a minimum dose of 37 MBq (1 mCi) for pediatric patients), preparation steps, and beyond use time following radiolabeling (6 hours) as the reference listed drug, Technescan MAG3.

We performed a risk assessment of the proposed prescribing information (PI), container label, carton labeling, and diagnostic radioassay 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, and diagnostic radioassay label for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection identified areas of vulnerability that may lead to medication errors. For the PI, we recommend removing the use of trailing zeros, including the appropriate units after all numeric values, removing the use of symbols and replacing them with their intended meanings, and revising the diluent names to the appropriate USP nomenclature. For the carton and container labels, we recommend revising the expiration date format, revising the package type term from [redacted] (b) (4)" to read "multiple-dose", and revising the storage information to include information regarding appropriate shielding for the radiolabeled product to protect from radiation. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Kit for the Preparation of Technetium Tc 99m Mertiatide Injection prescribing information (PI), vial container label, carton labeling, and diagnostic radioassay 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 Jubilant DraxImage Inc., dba Jubilant Radiopharma so that recommendations are implemented prior to approval of this NDA.

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

A. General Comments for Highlights of Prescribing Information and Full Prescribing Information

1. As currently presented, numeric values are presented with the use of trailing zeros. We recommend removing the use of trailing zeros in order to avoid any confusion. For example, in Table 1 under Section 2 Dosage and Administration, revise [redacted] (b) (4)".
2. We note there are numeric values presented throughout that are not immediately followed by the appropriate units. We recommend including the

appropriate units after all numeric values presented in the Prescribing Information.

3. As currently presented, there are symbols such as "-" and "~" to mean "to" and "about", respectively used throughout the PI. We recommend removing the use of the symbols and replacing them with their intended meanings.
4. As currently presented, the recommended dosage is presented in terms of mCi and mcCi. We recommend consistency among the recommended doses and presenting all recommended doses in terms of "MBq" with the "mCi" equivalent values presented in parentheses.

B. Highlights of Prescribing Information

1. Dosage and Administration
    a. We note the recommended dose range is presented as "185 MBq (5 mCi) to 370 MBq (10 mCi)". We recommend revising the recommended dose range to read "185 MBq to 370 MBq (5 mCi to 10 mCi)" in order to be consistent with currently approved radiopharmaceutical products.
    b. We note the route of administration is missing in the first two bullets. Revise the bullets to include the route of administration. For example, revise to "Recommended dose in adult patients is 185 MBq to 370 MBq (5 mCi to 10 mCi) as an intravenous bolus injection.".
    c. As currently presented, a bullet referring the end user to the full prescribing information is not present. We recommend adding a fourth bullet to the highlights of dosage and administration that reads "See Full Prescribing Information for radiation safety, drug preparation, administration, and radiation dosimetry information.".
2. Dosage Forms and Strengths
    a. We recommend removing the (b) (4) as this information is not needed here. Revise to read "Kit for the preparation of technetium Tc 99m mertiatide injection is supplied in a 10 mL multiple-dose vial containing 1 mg betiatide as a white lyophilized powder.".
    b. As currently presented, information regarding the radiolabeled drug product is not included. We recommend including information regarding the radiolabeled drug product in this section. We recommend including the statement "Upon radiolabeling with Technetium Tc 99m, it provides a clear, colorless solution containing (b) (4) to 3,700 MBq (100 mCi) technetium Tc 99m mertiatide in (b) (4) to 10 mL volume at calibration time.".

C. Prescribing Information

1. Section 2: Dosage and Administration

a. We note a section regarding radiation safety and drug handling is not present. We recommend including this information as the new Section 2.1 and making the recommended dosage section the new Section 2.2.

b. We note the use of the terms (b) (4)" and "(b) (4)". We recommend removing the use of these terms and replacing them with the approved USP names "0.9% Sodium Chloride Injection, USP" and "Sodium Pertechnetate Tc 99m Injection, USP" throughout the full prescribing information.

c. As currently presented, the recommended dose for adult and pediatric patients is presented together in the same paragraph. We recommend presenting this information as two separate lines in order to increase readability.

d. We note the first line of the recommended dosage section states "(b) (4) (b) (4)...". We recommend revising this statement to read "The recommended dose for adult patients is 185 MBq to 370 MBq (5 mCi to 10 mCi) as an intravenous bolus injection.".

e. We note the proposed Section 2 presents the administration information followed by the preparation information for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection. We recommend presenting the section regarding preparation prior to the section regarding administration information.

f. As currently presented, the Administration Instructions section does not include information regarding discarding any unused drug product. We recommend including a fourth bullet that states "Discard unused portion. Handle and dispose radioactive material in accordance with applicable regulations.".

g. We note the section regarding drug product preparation contains units of measure presented in terms of "MBq" and in terms of "GBq". Representing the product in two different units of measure that is incongruent may cause confusion. We recommend presenting the unit of measure in terms of "MBq" in order to avoid confusion. Revise "3.70 GBq" to read "3,700 MBq".

2. Section 3: Dosage Forms and Strengths

a. We recommend removing (b) (4) from this section as this information is not needed here. Revise to read "Kit for the preparation of technetium Tc 99m mertiatide injection is supplied in a 10 mL multiple-dose vial containing 1 mg betiatide as a white lyophilized powder.".

b. We note a physical description of the lyophilized powder is not included. We recommend including a physical description of the lyophilized powder in this section.

c. As currently presented, information regarding the radiolabeled drug product is not included. We recommend including information regarding the radiolabeled drug product in this section. We recommend including the statement "Upon radiolabeling with Technetium Tc 99m, it provides a clear, colorless solution containing [redacted] (b) (4) to 3,700 MBq (100 mCi) technetium Tc 99m mertiatide in [redacted] (b) (4) to 10 mL volume at calibration time.".

3. Section 16: How Supplied/Storage and Handling

a. As currently presented, the first line of Section 16.1 How Supplied reads "[redacted] (b) (4)". We recommend revising this section to read "Kit for the preparation of technetium Tc 99m Mertiatide Injection (NDC 65174-261-[redacted] (b) (4)) contains 1 mg betiatide as a lyophilized powder in multiple-dose vials packaged in cartons. Each carton contains 5 multiple-dose [redacted] (b) (4) vials, 5 [redacted] (b) (4) radioassay labels, 5 venting needles and [redacted] (b) (4)

b. We note the physical description of the lyophilized powder contained in each multiple-dose reaction vial is not presented. We recommend including a physical description of the lyophilized powder as part of Section 16.1 How Supplied.

c. We note the second paragraph under Section 16.1 How Supplied reads "[redacted] (b) (4)". We recommend revising this paragraph to read "The radionuclide is not part of Kit for the Preparation of technetium Tc 99m Mertiatide Injection. [redacted] (b) (4)

d. As currently presented, the storage information before and after radiolabeling are presented together in Section 16.2 Storage and Handling. We recommend including "Before radiolabeling" and "After radiolabeling" at the beginning of the respective storage statements in order to avoid confusion. Additionally, we recommend revising the storage information for the radiolabeled product to read "After radiolabeling, store Technetium Tc 99m Mertiatide upright in appropriate shielding to protect from radiation at room temperature 15°C to 30°C (59°F to 86°F). [redacted] (b) (4).".

4.2 RECOMMENDATIONS FOR JUBILANT DRAXIMAGE INC., DBA JUBILANT RADIOPHARMA

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

A. Vial Container Labels

1. As currently presented, the proposed vial container label states Kit for the Preparation of Technetium Tc 99m Mertiatide Injection is supplied in a "[redacted] (b) (4)". We recommend revising the package type to read "multiple-dose reaction vial".

2. We note the proposed vial container label does not include a statement regarding the route of administration following radiolabeling. We recommend including the statement "For intravenous use only after radiolabeling with Sodium Pertechnetate Tc 99m Injection, USP." on the proposed vial container label.

3. We note the proposed vial container label includes the statement "[redacted] (b) (4)". We recommend revising this statement to read "Recommended Dosage: See Prescribing Information".

4. As currently presented, the proposed vial container label includes the proposed format "YY MMM" for the expiration date. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

5. We note the proposed vial container label includes the statement "[redacted] (b) (4)" as part of the storage information. We recommend revising this statement to read "[redacted] (b) (4)

B. Carton Labeling

1. As currently presented, the top panel of the proposed carton labeling includes the statement "[redacted] (b) (4)". We recommend revising this statement to read "For intravenous use only after radiolabeling with Sodium Pertechnetate Tc 99m Injection, USP.".

2. We note the proposed back panel of the carton labeling defines the package type as "[redacted] (b) (4)". We recommend revising the package type term to read "multiple-dose [redacted] (b) (4) vial".

3. As currently presented, the proposed back panel of the carton labeling states that "[redacted] (b) (4)" is included. We recommend revising this to read "1 prescribing information".

4. We note the proposed carton labeling side panel includes the statement "[redacted] (b) (4)". We recommend revising this statement to read "Recommended Dosage: See Prescribing Information".

5. As currently presented, the proposed storage information presented on the side panel of the carton labeling includes reference to “(b) (4)” and “(b) (4)”. We recommend revising these statements to read “Before radiolabeling” and “After radiolabeling”.

6. We note the storage information presented on the side panel of the proposed carton labeling does not include information regarding storage of the radiolabeled drug product in proper shielding. We recommend revising the storage information for the radiolabeled drug product to read “After radiolabeling, store upright in appropriate shielding to protect from radiation at 15°C to 30°C (59°F to 86°F). (b) (4).”.

7. We note the side panel of the proposed carton labeling includes the statement “(b) (4)”. We recommend removing this statement as a statement (b) (4) is already included on the proposed carton labeling.

8. As currently presented, the proposed carton labeling includes the proposed format “YY MMM” for the expiration date. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

C. Diagnostic Radioassay Label

1. We note the proposed diagnostic radioassay label includes (b) (4) (b) (4) “Technetium Tc 99m Mertiatide Injection”. We recommend removing the “(b) (4) (b) (4) given this label will be used for the (b) (4) Additionally, we recommend removing the brackets around “Technetium Tc 99m Mertiatide Injection” and increasing the prominence of the drug product name.

2. As currently presented, the proposed diagnostic radioassay label includes placeholders for “date” and “time” information to be filled in. We recommend revising these placeholders to read “Calibration _______ Date ______ Time”.

3. We note the proposed diagnostic radioassay label contains a placeholder for “(b) (4)” information. We recommend revising this placeholder to read “Discard After: _______ Date ________ Time”.

4. We note the proposed diagnostic radioassay label includes the statement “(b) (4) (b) (4)”. We recommend revising this statement to read “(b) (4) (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection received on March 30, 2022 from Jubilant DraxImage Inc., dba Jubilant Radiopharma, and the listed drug (LD).

Table 2. Relevant Product Information for Kit for the Preparation of Technetium Tc 99m Mertiatide Injection and the Listed Drug

Product Name	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection	Technescan MAG3[a] NDA 019882
Initial Approval Date	N/A	June 15, 1990
Active Ingredient	[redacted] (b) (4)	
Indication	[redacted] (b) (4)	
Route of Administration	Intravenous	
Dosage Form	For Injection	
Strength	1 mg betiatide per vial	
Dose and Frequency	[redacted] (b) (4) and imaging studies is 185 MBq (5 mCi) to 370 MBq (10 mCi). In pediatric patients the recommended dose range is 2.6 MBq/kg (70 microCi/kg) to 5.2 MBq/kg (140 microCi/kg) with a minimum dose of 37 MBq (1 mCi).	
How Supplied	5 [redacted] (b) (4) vials. Each 10 mL of [redacted] (b) (4) [redacted] (b) (4) vial in lyophilized form contains: 1 mg of Betiatide, [redacted] (b) (4)	Technescan MAG3 is supplied as a lyophilized powder packaged in vials. Each reaction vial contains 1 mg betiatide, 0.05 mg (minimum) stannous chloride dihydrate ($SnCl_2 \cdot 2H_2O$), 0.2 mg (maximum) total tin expressed as stannous chloride dihydrate

[a] Technescan MAG3 [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2014 JUL 28. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019882

	[redacted] (b) (4)	($SnCl_2 \cdot 2H_2O$), 40 mg sodium tartrate dihydrate ($Na_2C_4H_2O_6 \cdot 2H_2O$), and 20 mg lactose monohydrate. The pH of the reconstituted drug is between 5.0 and 6.0. No bacteriostatic preservative is present. Packages containing 5 reaction vials (NDC 69945-096-20) are available.
Storage	Kit for the Preparation of Technetium Tc 99m Mertiatide should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F) and protected from light until use. The [redacted] (b) (4) vial should be stored at room temperature 15°C to 30°C (59°F to 86°F) and must be [redacted] (b) (4)	Technescan MAG3 should be stored at controlled room temperature 20° to 25°C (68° to 77°F) and protected from light until use. The reconstituted vial should be stored at room temperature (15° to 30°C) and must be used within six hours of preparation.

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Kit for the Preparation of Technetium Tc 99m Mertiatide Injection labels and labeling submitted by Jubilant DraxImage Inc., dba Jubilant Radiopharma.

- Vial Container Label received on March 30, 2022
- Carton Labeling received on March 30, 2022
- Diagnostic Radioassay Label received on March 30, 2022
- Prescribing Information (Image not shown) received on May 3, 2022, available from \\CDSESUB1\evsprod\nda216820\0004\m1\us\114-labeling\114a-draft-label\prescribing-information-uspi-plr-clean.pdf

G.2Label and Labeling Images

- Vial Container Label

(b) (4)

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

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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Division of Pediatrics and Maternal Health Review

Review Date:	September 28, 2022	**Date of Consult Request**:	June 2, 2022
From:	Christos Mastroyannis, M.D., Medical Officer, Maternal Health Division of Pediatrics and Maternal Health (DPMH)		
Through	Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH		
To:	Division of Imaging and Radiation Medicine (DIRM)		
NDA Number:	216820		
Drug:	Kit for the Preparation of Technetium Tc 99m Mertiatide		
Applicant:	Jubilant DraxImage Inc		

Indication: For use in the diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients. It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex.

Materials Reviewed

- Applicant's submission of March 30, 2022
- Division's Consult request of June 2, 2022, in DARRTS and Reference ID: 4993106
- Labeling Review of Nephroscan (kit for the preparation of technetium Tc 99m succimer injection), NDA 214993 Reference ID: 4872868 by Catherine Roca, MD [1]
- Labeling Review of [redacted] (b) (4) NDA 022335, Reference ID: 4702466 by Jane Liedtka, MD.[1]
- Labeling Review for Draximage MAA (kit for the preparation of technetium Tc 99m albumin aggregated injection), NDA 017881, Reference ID: 4875640 by Carrie Ceresa, Pharm D., MPH[1]
- Prior internal DPMH email communications of October 13, 2021 with Kish Chakrabarti,

[1] DPMH did not rely on data in these NDAs or the Agency's finding of safety and effectiveness from these NDAs to support labeling sections of this Kit for the Preparation of Technetium Tc 99m Mertiatide NDA. Rather, the cross-reference to these NDAs is included to avoid duplicating background information relevant to this class of products.

Ph.D., a health physicist with DIRM

BACKGROUND

Regulatory History

The applicant, Jubilant DraxImage Inc., submitted NDA 216820 for Kit for the Preparation of Technetium Tc 99m Mertiatide on March 30, 2022. Technetium Tc 99m Mertiatide is indicated for use in the diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients. It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex. The applicant has submitted this original application for approval under the 505(b)(2) pathway. DIRM has requested DPMH to assist with the labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

[redacted] (b) (4)

[redacted] (b) (4) Characteristics[2]

[redacted] (b) (4)

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.

Physical Decay Chart: Technetium Tc 99m, Half-life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

* Calibration Time

Technetium Tc 99m Mertiatide is [redacted] (b) (4) plasma protein bound following intravenous injection. The protein binding is reversible.[3]

REVIEW

This submission does not contain any clinical data, it provides only CMC data. In discussions with the Division, it was decided that no information request (IR) for literature search was needed because the safety for technetium has been established over the years. DPMH Maternal Health Team has evaluated different Technetium Tc 99m products in the past, such as Nephroscan, NDA 214993 Reference ID: 4872868 by Catherine Roca, MD; Technegas, NDA 022335, Reference ID: 4702466

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[2] Proposed labeling as of May 3, 2022.

[3] From applicant's proposed labeling in [redacted] (b) (4)

by Jane Liedtka, MD; and Draximage MAA NDA 017881, Reference ID: 4875640 by Carrie Ceresa, Pharm D., MPH.

Pregnancy

No animal reproductive studies have been conducted with Technetium Tc 99m Mertiatide. .The findings from available data found in published literature related to Technetium Tc 99m and use in pregnant women are insufficient to inform a drug associated risk for major birth defects and miscarriage; however, radiation exposure to the fetus from technetium Tc99m is expected to be low (less than 0.50 mGy). No adverse fetal effects or radiation-related risks have been identified for diagnostic procedures involving less than 50mGy, which represents less than 10mGy fetal doses.,[4] Technetium Tc99m has been used for many decades, so it is likely that there have been a number of fetal exposures since that time, yet there are few published adverse events reported.
A pregnancy postapproval safety study is not recommended.

Lactation

There are no data on the presence of technetium Tc 99m Mertiatide in breast milk, the effects of technetium Tc 99m Mertiatide on the breastfed infant or the effects on milk production. Limited data from case reports indicate that technetium 99m is present in low amounts in breast milk following injection of various 99m Tc-labeled radiopharmaceuticals (i.e., pertechnetate, plasmin, methylene diphosphonate (MDP), diethylenethiaminepentaacetic acid (DTPA), macroaggregated human serum albumin (MAA), red blood cells).[5] Technetium Tc 99m Mertiatide Injection is used for imaging in infants 30 days of age and older with renal disease. Exposure to technetium Tc 99m mertiatide via breast milk is expected to be lower than the therapeutic/diagnostic dose. This statement has been approved by Lynne Yao, MD, Director DPMH and agreed by DIRM. A publication by Evans, JL *et. al*.[6] corroborates this statement when the authors evaluated two breastfeeding mothers. They estimated up to 1.6% of the maternal administered activity would be ingested by the infant. That would be 0.16 mCi for the maximum adult administered activity of 10 mCi. While the data are limited, the estimate is well below the minimum administered activity for pediatric patients of 1 mCi. DPMH is in agreement with DIRM from previous discussions and agrees to adopt the Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials,[7] which states that for 99mTc a 24- hour interruption of breastfeeding is recommended after a dose limit of 0.1 rad administration.

Females and Males of Reproductive Potential

There are no human or animal data available on the effects of Technetium Tc 99m on fertility to inform a potential clinical risk or any effects on hormonal contraception. In addition, pregnancy testing and contraception recommendations are not warranted; therefore, this subsection will be omitted from labeling.

CONCLUSION

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[4] ACR-SPR Practice Parameter for Imaging Pregnant of Potentially Pregnant Adolescents and Women with Ionizing Radiation. Revised 2018 (Resolution 39), pp1-23.

[5] Ahlgren L, Ivarsson S, Johansson L, Mattsson S, and Nosslin B. Excretion of Radionuclides in Human Breast Milk After the Administration of Radiopharmaceuticals. J Nucl Med 26:1085-1090, 1985

[6] Evans JL, Mountford PJ, Herring AN, and Richardson MA: Secretion of radioactivity in breast milk following administration of Tc99m-MAG3, Nuclear Medicine Communications, (1993) 14, 108-111

[7] Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, Final Report, dated January 31, 2019.

Pregnancy

There are no data with Technetium Tc99m Mertiatide use in pregnant women to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal reproduction studies with technetium Tc99m Mertiatide have not been conducted. Although all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose, the radiation exposure to the fetus from technetium Tc99m Mertiatide is expected to be low.

Lactation

Limited data from case reports indicate that technetium Tc99m is present in breast milk in low amounts. However, exposure of a breastfed infant to radiation from technetium Tc99m can be minimized by discontinuing breastfeeding for 24 hours according to current guidelines. Instructions for discontinuing breastfeeding and pumping and discarding of breastmilk for a minimum of 24 hours will be included in labeling.

Females and Males of Reproductive Potential

There are no human or animal data available on the effects of technetium Tc99m on fertility or the effects on hormonal contraception. Practice parameters for technetium Tc99m do not require pregnancy testing or contraception. Therefore, subsection 8.3 will not be included in labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

(b) (4)

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