CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213227Orig1s000

OTHER REVIEW(S)

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:	August 27, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 213227
Product Name and Strength:	Detectnet (copper Cu 64 dotatate) injection, 148 MBq (4 mCi) per 4 mL at calibration (37 MBq (1 mCi) per 1 mL)
Applicant/Sponsor Name:	RadioMedix Innovating Theranostics (RadioMedix Inc.)
OSE RCM #:	2019-1492-2
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

RadioMedix Inc. submitted revised vial container labels and carton labeling received on August 26, 2020 for Detectnet (copper Cu 64 dotatate) injection NDA 213227. We reviewed the revised vial container labels and carton labeling for Detectnet (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] Kane, D. Label and Labeling Review for Detectnet (NDA 213227). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 24. RCM No.: 2019-1492-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 26, 2020

Vial Container labels

(b) (4)

Carton Labeling

(b) (4)

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/s/

DEVIN R KANE
08/27/2020 11:44:19 AM

HINA S MEHTA
08/27/2020 03:32:00 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:	August 24, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 213227
Product Name and Strength:	Detectnet (Copper Cu 64 Dotatate) injection, 148 MBq (4 mCi) per 4 mL at calibration (37 MBq (1 mCi) per 1 mL)
Applicant/Sponsor Name:	RadioMedix Innovating Theranostics (RadioMedix Inc.)
OSE RCM #:	2020-1492-1
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

RadioMedix Inc. submitted revised vial container label and carton labeling on June 29, 2020 for Detectnet (copper Cu 64 Dotatate) injection NDA 213227. We reviewed the revised vial container label and carton labeling for Detectnet (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 and carton labeling are unacceptable from a medication error perspective. We refer to the Proprietary Name Decision Letter dated August 18, 2020 finding the proposed proprietary name, Detectnet, conditionally acceptable[b]. We note the presentation of the proprietary name in mixed case type presentation. We provide recommendations for RadioMedix Inc. below.

[a] Kane D. Label and Labeling Review for (b) (4) (NDA 213227). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 18. RCM No.: 2019-1492.
[b] Harris, D. Proprietary Name Granted for NDA 213227, Detectnet (copper Cu 64 Dotatate). Silver Spring (MD): FDA, CDER, OSE (US); 2020 AUG 18.

3 RECOMMENDATIONS FOR RADIOMEDIX INNOVATING THERANOSTICS (RADIOMEDIX INC.)

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

A. General Comments for Vial Container Label and Carton Labeling

1. We note that the presentation of the proprietary name on the proposed vial container label and carton labeling have the letter string "net" presented (b) (4) [redacted] Thus, we recommend that the proprietary name is presented as Detectnet on the vial container labels and carton labeling.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 29, 2020

Vial Container Labels

Carton Labeling

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/s/

DEVIN R KANE
08/24/2020 11:32:13 AM

HINA S MEHTA
08/24/2020 05:43:25 PM

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

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

Memorandum

Date: July 22, 2020

To: Brenda Ye, M.D.
Division of Imaging and Radiation Medicine (DIRM)

Modupe Fagbami, Regulatory Project Manager, DIRM

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) (copper Cu 64 dotatate injection), for intravenous use

NDA: 213227

In response to DIRM's consult request dated January 24, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for (b) (4)

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DIRM on July 20, 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 July 22, 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.

15 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
07/22/2020 04:28:23 PM

NDA 213227

Comments Regarding Prescribing Information on Radiation Dosimetry and Lactation for Women Administered Cu 64-DOTATATE.

Kish Chakrabarti, Ph.D, FAAPM

INDICATIONS AND USAGE

(b) (4) is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adults.

Summary:

Radiation dosimetry: Radiopharmaceutical absorbed doses in various organs indicate that critical organs are the adrenals, kidney and liver. However, the dose values are not unusually large, and they raise no safety concern. No information, however, is provided on contributions to absorbed dose from associated CT scans.

Lactation: For the recommended Cu 64 DOTATATE activity (148 MBq) administered to a breast-feeding woman, we estimate that without interruption of a newborn infant's feeding schedule, an upper limit to the total newborn effective dose would be approximately 0.92 mSv. This value is very close to the NRC-recommended safeguard ceiling of 1 mSv. Since the modeling applied contains much uncertainty, as a safety precaution we recommend that following radiopharmaceutical administration, breast feeding be interrupted for an interval of twelve hours, which would nearly halve the estimated newborn effective dose to 0.48 mSv. Contrary to the sponsor's proposal to interrupt breast feeding (b) (4) our approach provides a safety factor of approximately 2, balances safeguarding against radiation detriment versus constraining the benefit of breast feeding, and promotes the optimization of radiation dose in accord with national and international standards.

Review:

Radiation Dosimetry

The mean values of the estimated radiation absorbed doses (per unit administered activity) for adults receiving copper Cu 64 DOTATATE are shown in Table 1.

Table 1. Estimated Radiation Absorbed Dose for Copper Cu 64

Target Organ	Mean* absorbed dose (mGy/MBq)
Adrenals	0.137
Brain	0.013
Breasts	0.013
Gallbladder wall	0.040
Lower large intestine wall	0.043
Small intestine	0.066
Stomach wall	0.019
Upper large intestine wall	0.022
Heart wall	0.019
Kidneys	0.139
Liver	0.161
Lungs	0.017
Muscle	0.019
Ovaries	0.019
Pancreas	0.093
Red Marrow	0.027
Osteogenic cells	0.034
Skin	0.012
Spleen	0.115
Testes	0.014
Thymus	0.015
Thyroid	0.014
Urinary bladder wall	0.037
Uterus	0.019
Total body	0.025
Effective dose (mSv/MBq)	0.032

* Mean of 5 patients.

The critical organs are the adrenals, kidney and liver.

Whole-body PET scans [1] (skull to mid thigh) were obtained in 3-dimensional mode, with an acquisition time of 3 min per bed position. CT data were used for attenuation correction. A diagnostic CT [1] scan was obtained before the first PET scan, with a 3-mm slice thickness, 120 kV, and 225 mAs. A low-dose CT scan [1] (20 mAs, 140 kV or 2.5 mAs, 140 kV) was acquired before each of the subsequent PET scans and used for attenuation correction. No information is provided from CT scan doses. **It is important that we receive CT doses also in order to estimate and evaluate total patient doses properly.**

Lactation:

Sponsor's labeling: "Advise a lactating woman to interrupt breastfeeding, (b) (4) after administration in order to minimize radiation exposure to a breastfed infant."

Modelling and calculations of dose

For the nursing infant, the exposure comes internally, from the ingested radioactive milk, and externally, from exposure to the mother who is a radiation source in close proximity to the infant during nursing.

- **External Maternal Radiation to the Nursing Child**

The time-integrated activity (also known as the cumulated activity or residence time) in the lactating breast results from radiopharmaceutical secretion into breast milk and was estimated by Stabin and Breitz [2].

During breast feeding, activity within the infant changes as the pharmaceutical is metabolized, as radioactivity is distributed within the woman and excreted into breast milk, and as the physical decay of the radioisotope proceeds:

$A(t) = A(0) \times \sum_n \exp[(-0.693 \times (t_n - t_i)/(T_{eff})]$

t_i = time (h) at which the activity reaches a maximum, i.e., that is peak concentration

$t_n = t_i + 4n$, n=0, 1, 2, ...

Cumulated activity $An = A(t) \times f \times 1.44 \times T_{eff}$, f is fraction of activity, T_{eff} effective half life.

Dose is calculated as MIRD schema and OLINDA program.

$D_{rk} = \sum An\ S(r_k \leftarrow r_h)$

Dose to the infant is calculated using Equation (1) and (2) based on Vasken Dilsizian et al. [3], *Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials.*

There are several uncertainties in the current measurements and calculations because of lack of data and published information for 64 Cu DOTATATE. No breast PET imaging with uptake information after administration of 64 Cu, and no biokinetics is available; neither are maximum breast activity, Φ, biological life time, and other parameters needed for appropriate determination of infant dose during breast feeding.

In lactating breasts, enhanced uptake and secretion into breast milk may occur with certain radiopharmaceuticals and possibly their radioactive metabolites.

For radiopharmaceuticals for which relevant data were not available (as is the case of the 64 Cu DOTATATE), it was conservatively assumed [3] that the effective half-life of activity in breast milk and in the maternal remainder of body, respectively, equaled the physical half life of the radioisotope.

In absence of any uptake of activity data, we calculated dose assuming both activity at **three hours** and **one hour** peaks for comparison, and feeding at 4 hours interval thereafter as every 4 hours of feeds. We took the calculations up to t_n = 100 hours.

Doses from the mother breast to the infant as well as remainder part of the mother to the infant are calculated. The external absorbed dose to the nursing child from activity in the maternal breast and the external absorbed dose to the nursing child from activity in the maternal remainder of body (assumed to be equivalent to the maternal torso) are two main sources of doses.

These are calculated using radionuclide residence times (τ) in the breast milk, $\tau_{\text{maternal breast}}$, and in the maternal remainder of body, $\tau_{\text{maternal rem}}$, using ref.[3] Equations (4) and (5), respectively, and calculations of decay of activities using the equation for A(t) above. However, for Effective Dose, we used $f_{\text{breast milk}}$ (64 Cu Dotatate)|max ≈ maximum absorbed absorbed-energy ratio = 0.0053 from the administered activity as described below.

When the residence times τ are inserted in ref.[3] equations 2 and 3, the following values for the external contributions to infant effective dose are obtained from cumulative exposure (through multiple feeding sessions), respectively, to activity in the maternal breast and activity in the remainder of the maternal body.

The values are added as follows to yield the total external contribution to infant effective dose (ED):

0.06 + 0.48 = 0.54 mSv

- **Internal Radiation Dose to the Nursing Child from Ingestion of Radioactive Milk**

For internal dose, effective dose from the preceding table is used, and the ratio of masses with ED were calculated [6].

Mean absorbed doses (mGy/MBq) for different organs in the preceding table were used and multiplied by the respective organ mass (g). These products result in adult absorbed energy per unit administered activity (μJ/MBq).

Target-organ absorbed energy per unit administered activity summed over all organs involved provides fraction of total energy absorbed: This fraction is obtained as the ratio of energy per unit administered activity (μJ/MBq) in the adult breast divided by the sum over all adult organ absorbed energies (μJ/MBq). The value of this fraction for the breast is 0.0053 for from 64 Cu-dotatate.

Using the mother's weight as 60 kg and infant's as 4 kg, 185 MBq administered activity of 64 Cu-dotatate, the effective dose to the child is calculated to be 0.38 mSv from ingestion of breast milk. That would be the maximum internal dose to a nursing child.

Hence the total effective dose to the infants from internal plus external radiation exposure: 0.38 + 0.54 = 0.92 mSv

Discussion and recommendations:

Based on the criterion that the maximum effective dose equivalent to a breast-feeding newborn infant be less than 1 mSv (0.1 rem), Table 3 of RG 8.39 pp. 11 [7] delineates activities of radiopharmaceuticals administered to breast-feeding mothers above which medical licensees are required to provide instructions to patients that include information on the interruption or discontinuation of breast-feeding and are required to maintain records of the basis for patient release. Table 3 of RG 8.39 also includes examples of recommended durations of interruption of breast-feeding.

0.92 mSv is the estimated maximum effective dose that an infant can receive during breast feeding. However, this value has much uncertainty. Without knowledge of biological excretion into breast milk, for the relatively long physical-decay half-life (12.7 h) of 64 Cu as a positron emitter, it is plausible that a significant amount of activity remains in breast milk for several hours following administration, possibly leaving the infant particularly vulnerable during this early period. In 27 hours the activity goes down to 25% of the peak value. External dose is 0.09 mSv after 27 hours have elapsed were the infant to start breast feeding and continues every 4 hours after that. The dose is 0.14 mSv after 11 hours have elapsed and were the infant to continue every 4 hours. Internal dose reduces because administered activity (185 MBq) is reduced to 50 % (0.19 mSv) and 25% (0.09) respectively.

Total dose after 11 hours	**0.19 + 0.14 = 0.33 mSv**
After 27 hours	**0.09 + 0.09 = 0.18 mSv**

It is therefore recommended that the breast feeding be interrupted **by 12 hours** after administration of 64 Cu DOTATATE. This interval of interruption would ensure that the infant dose remains well within the 1 mSv ceiling.

References:

[1] Andreas Pfeifer et al. Clinical PET of Neuroendocrine Tumors Using 64Cu-DOTATATE: First-in-Humans Study. Journal of Nuclear Medicine, Vol. 53, No. 8 pp 1207-1215, 2012

[2] Michael G. Stabin and Hazel B. Breitz, "Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings, and Radiation Dosimetry," The Journal of Nuclear Medicine, Vol. 41, No. 5, pp. 863-873, May 2000.

[3] Vasken Dilsizian et al., Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, Report dated February 1, 2018; revised June 19, 2018; submitted June 26, 2018; re-revised September 20, 2018; endorsed

[4] in a unanimous vote by ACMUI September 20, 2018; final report submitted January 31, 2019;

https://www.nrc.gov/docs/ML1903/ML19038A498.pdf; accessed May 11, 2020.

[5] Meeting Summary (https://www.nrc.gov/docs/ML1828/ML18288A691.pdf), Meeting of the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI), September 20 – 21, 2018.

[6] Michael G. Stabin, Richard Perks and Erin Crowe, OLINDA/ DOSE EXAM: second generation of personal computer software for internal dose assessment in nuclear medicine, Journal of Nuclear Medicine, Vol. 46, No. 6, pp. 1023-1027, 2005

[7] U.S. Nuclear Regulatory Commission, Regulatory Guide 8.39 Revision 1, Release of Patients Administered Radioactive Materials, April 2020, accessed May 11, 2020 via https://www.nrc.gov/docs/ML1923/ML19232A081.pdf.

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/s/

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ALEXANDER GOROVETS
07/20/2020 11:20:19 AM

Clinical Inspection Summary

Date	6/24/2020
From	Christian Shenouda, M.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Brenda Ye, M.D., Clinical Reviewer August Hofling, M.D., Clinical Team Leader Modupe Fagbami, Regulatory Project Manager Division of Medical Imaging (DMI)
NDA	NDA 213227
Applicant	RadioMedix, Inc.
Drug	(b) (4) (64Cu-DOTATATE)
NME	Yes
Proposed Indication(s)	Use in Positron Emission Tomography (PET) imaging for the localization of somatostatin receptor positive Neuroendocrine Tumors (NET).
Consultation Request Date	1/29/2020
Summary Goal Date	7/1/2020
PDUFA Date	9/3/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical site of Dr. Rodolfo Nunez was inspected in support of application NDA 213227. Based on the results of this inspection, the study RMX-18-22 appears to have been conducted adequately, and the data generated by this site appears acceptable in support of the respective indication. The data used to generate the primary outcome measure was verifiable, and there was no evidence of underreporting of adverse events.

II. BACKGROUND

The sponsor, RadioMedix, Inc., has submitted the results of a Phase 3 efficacy trial, Protocol RMX-18-22, to support the use of (b) (4) (64Cu-DOTATATE) for the use in Positron emission tomography (PET) imaging in the localization of somatostatin receptor positive NET.

Protocol RMX

Title: " An Open-label, Single-dose, Single-arm, Single-center Clinical Trial of 64 Cu-DOTATATE (NETMedix™) PET-CT Scan for Imaging Patients with Known or Suspected Somatostatin Receptor-positive Neuroendocrine Tumors (NETs)"

Subjects: 63 subjects of which 62 had a dose of 4 mCi ± 10 of 64Cu-DOTATATE (29 healthy controls and 33 with confirmed or suspected disease)

Sites: 1 US study site

Study Initiation and Completion Dates: January 22, 2018 to December 2, 2018

This was an open-label, single-dose, single-arm, single-center imaging study using the DOTATATE peptide, labelled with the 64 Cu tracer. The duration of subject participation was from the time of signing the informed consent form through a 2-day post-injection visit.

Imaging data from the PET-CT scan were transferred to a Clinical Research Organization (CRO) (b) (4) who performed blinding and randomization of the images that were then provided to three raters. Raters categorized images as "Disease" or "No Disease" based on uptake of the radiotracer in tumor tissue. If the scans were categorized as "Disease", the physicians further categorized the readings as "Localized" or "Metastatic" disease.

Sensitivity and specificity were calculated by comparing raters' assessment to a Standard of Truth (SOT) measure to evaluate the rate of true positive, true negative, false positive and false negative. The SOT reference was an assessment by an independent oncologist who used non-investigational methods (histopathological or accepted imaging modalities) to determine the presence or absence of disease.

The co-primary efficacy endpoints were the sensitivity and specificity of 64Cu-DOTATATE PET-CT imaging when each imaging readers' subject-level result was compared to a SOT for the subject, with primary endpoint success defined as the same two out of three readers having sensitivity and specificity results exceeding the specified thresholds (sensitivity >70% and specificity >60%).

Rationale for Site Selection

The following clinical investigator (CI) site was chosen for inspection as it was the only site for this clinical trial.

III. INSPECTION RESULTS

1. Rodolfo Nunez, M.D
Excel Diagnostics and Nuclear Oncology Center
9701 Richmond Ave.
Houston, TX 77042

Inspection Dates: May 4 to May 8, 2020

At this site for Protocol RMX-18-22, 64 subjects were screened and 59 were enrolled, all of whom completed the study. This inspection reviewed subject-specific study records including, but not limited to, informed consent forms, adverse event reporting, and primary efficacy endpoint source data. Study documents related to compliance, medication storage/accountability, IRB communications, and monitoring were also reviewed.

The inspection reviewed the records of 63 of the 64 screened subjects. Certified copies of the radiology reads and standard of truth (SOT) imaging were sent to the site prior to the inspection. The imaging data used to calculate sensitivity and specificity were verified against the data line listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

Christian N. Shenouda, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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CC:

Central Doc. Rm. NDA 213227

DMI Review Division /Division Director/Libero Marzella
DMI Review Division /Medical Team Leader/ August Hofling
DMI Review Division /Project Manager/ Modupe Fagbami
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OSI/ GCP Program Analysts/ Yolanda Patague
OSI/Database PM/Dana Walters

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: June 9, 2020 **Date Consulted:** April 6, 2020

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Medical Imaging and Radiation Medicine (DMIRM)

Drug: ^{64}CU-Dotatate Injection

NDA: 213227

Applicant: Radiomedix, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: "for use with positron emission tomography (PET) for (b) (4) localization (b) (4) (b) (4) of somatostatin receptor positive neuroendocrine tumors (NETs) in adults"

Materials Reviewed:

- Applicant's proposed labeling, 1/3/2020

Consult Question: Please review Pregnancy and Lactation Labeling Rule (PLLR) subsections of labeling.

INTRODUCTION AND BACKGROUND

On January 3, 2020, Radiomedix, Inc. submitted the final modules for ^{64}CU-Dotatate Injection, NDA 213227, an original 505(b)(2) rolling review application, indicated for use with positron emission tomography (PET) for (b) (4) localization (b) (4) of somatostatin receptor positive neuroendocrine tumors (NETs) in adults. The Division of Medical Imaging and Radiation Medicine (DMIRM) consulted the Division of Pediatric and Maternal Health (DPMH) on April 6, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

There are no previous DPMH reviews for ^{64}CU-Dotatate Injection.

Regulatory History

- 5/18/2016: Orphan Designation granted for ^{64}CU-Dotatate for the management of neuroendocrine tumors (NETs);
- 12/19/2018: Fast track designation granted;
- 6/27/2019: Rolling review of NDA submission granted;
- 7/8/2019: Initial modules of NDA submitted; Priority review requested;
- 1/3/2020: remaining modules of NDA submitted; application filed on 3/3/2020.

^{64}CU-Dotatate Drug Characteristics[1]

- A radioactive copper diagnostic agent; a ß+ radionuclide that binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSTR2), including malignant cells which over express SSTR2.
- Dotatate is an amino acid peptide, with a covalently bonded DOTA bifunctional chelator; can be bound with radionuclides to form radiopharmaceuticals for PET imaging or radionuclide therapy.[2]
- "^{64}CU has a unique decay profile and can be used for positron emission tomography imaging and radionuclide therapy. The well-established coordination chemistry of copper allows for its reaction with different types of chelator systems. It can be linked to antibodies, proteins, peptides, and other biologically relevant small molecules."[3]
- ^{64}CU decays with a half-life of 12.7 hours.
- Metabolic fate is unknown; however, structurally similar analogs do not undergo metabolism and are excreted as parent compounds.
- Estimated radiation absorbed dose (based on the recommended administered dose) to the uterus is 0.019 mGy/MBq and to the breasts is 0.013 mGy/MBq.
- Radiation is a carcinogen and mutagen.
- Radiation dosimetry: estimated radiation absorbed doses of ^{64}CU-Dotatate in various organs (see Table 1 below from proposed ^{64}CU-Dotatate labeling).

[1] Refer to applicant proposed labeling, 1/3/2020
[2] https://en.wikipedia.org/wiki/DOTA-TATE
[3] Zhou Y, et al.^{64}Cu-based Radiopharmaceuticals in Molecular Imaging, Tech Cancer Res Treat, 2019; 18:1-10

Table 1. Estimated Radiation Absorbed Dose for Copper Cu 64

Target Organ	Mean* absorbed dose (mGy/MBq)
Adrenals	0.137
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Upper large intestine wall	0.022
Heart wall	0.019
Kidneys	0.139
Liver	0.161
Lungs	0.017
Muscle	0.019
Ovaries	0.019
Pancreas	0.093
Red marrow	0.027
Osteogenic cells	0.034
Skin	0.012
Spleen	0.115
Testes	0.014
Thymus	0.015
Thyroid	0.014
Urinary bladder wall	0.037
Uterus	0.019
Total body	0.025
Effective dose (mSv/MBq)	0.032

* Mean of 5 patients.

Diagnostic Imaging During Pregnancy

The International Radiation Protection Association (IRPA) [4] states that pregnancy is not a reason to withhold necessary imaging procedures in pregnant women as most of the commonly used radiopharmaceuticals (I 131 is an exception) result in low fetal radiation doses and pose little risk to the fetus or later in childhood. The benefits of nuclear imaging procedures in a pregnant woman usually outweigh the minimal risks associated with small amounts of radiation exposure to the fetus.

The International Commission of Radiological Protection (ICRP)[5] states:

- For most pregnant patients, radiation exposure that is medically appropriate produces minimal radiation risk to the fetus.
- There are radiation - related risks throughout pregnancy that are related to the stage of pregnancy and absorbed radiation dose.
- Radiation risk is most significant during organogenesis and early fetal period, less in the 2nd trimester, and least in the 3rd trimester.
- Malformations have a threshold at 100-200 mGy and are typically CNS-related.
- Fetal radiation doses of 1000 mGy can result in severe mental retardation and microcephaly, especially with exposure during weeks 8-15 of gestation.
- There is a slight increase in cancer risk with a fetal radiation dose of 10 mGy.
- Most diagnostic procedures are done with short-lived radionuclides that cause low fetal radiation doses. The fetal radiation dose may be reduced through maternal hydration and encouraged voiding of urine with these procedures.

The ICRP also states:[6]

- The absorbed dose to the uterus may be used as a substitute for the absorbed dose to the embryo/fetus during the 1st trimester of pregnancy.
- The absorbed dose to the fetus from radioactive substances without placental transfer is expected to be in the same range as the dose to the uterus.
- For radioactive substances with placental transfer, the absorbed dose to maternal organs and tissues may be representative of the absorbed dose to the corresponding fetal organs and tissues.

The American College of Obstetricians and Gynecologists (ACOG)[7] states that:

- Imaging procedures should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient.
- With few exceptions, radiation exposure through radiography, computed tomography (CT) scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary for a diagnosis in question, they should not be withheld from a pregnant woman.

[4] Refer to www.irpa.net
[5] Refer to www.icrp.org Publication 84, Pregnancy and Medical Radiation
[6] Refer to www.icrp.org Publication 106, Radiation Dose to Patients from Radiopharmaceuticals
[7] ACOG Committee Opinion, Committee on Obstetric Practice: Guidelines for Diagnostic Imaging During Pregnancy and Lactation, Number 723; October 2017

- ACOG describes the effects of gestational age and radiation dose of radiation induced teratogenesis and the fetal radiation doses associated with common radiological examinations (see Appendix 1).

Diagnostic Imaging During Lactation

Most radiopharmaceuticals are present in breastmilk; therefore, unless there are data that demonstrate otherwise, some radioactive compound will be measured in breastmilk after administration of a radiopharmaceutical. Radiopharmaceutical uptake by the breast is fairly rapid with peak concentrations at 3 to 4 hours after administration. A radiopharmaceutical's concentration in the maternal circulation is generally proportional to its concentration in breast milk. Individual radionuclide dose concentrations vary tremendously, mainly due to a variability in breast tissue mass among women; therefore, it would be ideal to obtain breastmilk samples from individual patients to make the best recommendation for the time, if needed, to interrupt breastfeeding. Breastfeeding should be interrupted to limit an effective radiation dose of 1 mSv to the breastfed infant. Computer modeling can be used to determine the time, if any, needed to interrupt breastfeeding with specific radiopharmaceuticals. Nuclear Regulatory Commission (NRC) regulations (10CFR 35.75) require that if a nursing mother continues to breastfeed after receiving a radiopharmaceutical and the breastfed infant's radiation exposure could exceed an effective dose equivalent of 1 mSv, written instructions must be given to the mother regarding the potential adverse consequences if breastfeeding is not interrupted or ceased, as well as guidance on the discontinuation of breast-feeding. [8,9,10,11]

REVIEW

Neuroendocrine Tumors (NETs)

Neuroendocrine cells have traits similar to nerve cells and to the hormone-producing cells of the endocrine glands. Neuroendocrine tumors (NETs) are rare and the main primary sites are the gastrointestinal tract (62–67%) and the lung (22–27%). Presentation with metastatic disease accounts for 12–22% of cases. NETs can be slow-growing or aggressive and metastatic, often to the liver and bone. NETs may secrete higher-than-normal amounts of hormones, which can cause conditions including diabetes, flushing, and diarrhea. Types of NETs include carcinoid tumors, islet cell tumors, medullary thyroid carcinomas, pheochromocytomas, and neuroendocrine carcinomas of the skin (Merkel cell cancer).

Treatment depends on the type of tumor and its location, whether it produces excess hormones, how aggressive it is, and whether it has metastasized. Advances in treatment have improved the length of survival for patients with NETs. Treatment modalities include surgical resection, liver-directed therapy, somatostatin analog therapy, and chemotherapy and targeted agents.

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[8] Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, 6/26/2018, https://www.nrc.gov/docs/ML1817/ML18177A451.pdf

[9] Refer to www.icrp.org Publication 106, Radiation Dose to Patients from Radiopharmaceuticals

[10] Leide-Svegborn S, Ahlgren L., et al. Excretion of radionuclides in human breast milk after nuclear medicine examinations and recommendations on breastfeeding interruption, *Eur J Nucl Med Mol Imaging*, 2016; 43:808-821

[11] US Nuclear Regulatory Commission Regulatory Guide 8.39: Release of Patients Administered Radioactive Materials, April 1997

NETs account for only 0.5% of all malignancies. The incidence of NETs is approximately 2/100,000 with approximately 12,000 cases diagnosed each year in the U.S. with a rising incidence in the last several decades, which may be due to more awareness, improved diagnostic tools, or a change in definition. NETs are slightly more common in women than men and can occur at any age; however, they rarely occur in children.[12,13]

Due to the rarity of NETs, few pregnancies have been reported in women with the condition. Successful pregnancies have been reported in women with stable NETs, especially if surgical resection and chemotherapy and targeted therapy can be withheld during pregnancy, if women can be managed on somatostatin analogs, or in women who don't require ongoing treatment. The presence of metastatic carcinoid disease in a pregnant woman can lead to fetal demise. Maternal hypoglycemia, associated with an insulinoma, can also result in fetal demise during pregnancy. Lactating women with NETs can successfully breastfeed with a stable condition and during treatment with somatostatin analogs. Women with progressive NETs and those who require treatment with chemotherapy or targeted therapies will likely receive recommendations not to breastfed due to potential drug adverse effects in a breastfed infant.[14]

Pregnancy, Lactation, and females and Males of Reproductive Potential

Nonclinical Experience

Animal reproduction studies were not conducted

Postmarketing Experience

^{64}CU-Dotatate Injection is an investigation radiopharmaceutical and is not approved in any country for marketing.

Review of Literature - Applicant

No pregnancies, lactation information, or fertility effect information were reported in any of the published studies with ^{64}CU-Dotatate Injection.

DPMH conducted a search of available published articles in Embase, PubMed, LactMed[15] and *Medications in Mothers' Milk*[16] regarding the use of ^{64}CU-Dotatate Injection in pregnancy or lactation, any fertility effects with the use of ^{64}CU-Dotatate Injection. No relevant publications were found

[12] http://www.snmmi.org/Patients/Disease_Condition/Content.aspx?ItemNumber=13952&navItemNumber=13231
[13] https://www.cancer.net/cancer-types/neuroendocrine-tumors/statistics
[14] Sherf S, Yu R. Gut and pancreatic Neuroendocrine tumors in pregnancy and lactation. https://www.sciencedirect.com/science/article/pii/B9780128148235000246?via%3Dihub
[15] https://toxnet nlm nih.gov/newtoxnet/lactmed.htm
[16] Hale T. Medications and Mothers' Milk. Springer Publishing Co. 2017

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no data available with the use of ^{64}CU-Dotatate Injection in pregnant women; however, ACOG,[17] IRPA,[18] and ICRP[19] all state that pregnancy is not a reason to withhold necessary imaging procedures in pregnant women as most of the commonly used radiopharmaceuticals (I 131 is an exception) result in low fetal radiation doses and pose little risk to the fetus. Radiation risk is most significant during organogenesis and early fetal period and lessens as pregnancy progresses. The ICRP states the absorbed dose from a radiopharmaceutical to the uterus may be used as a substitute for the absorbed dose to the embryo/fetus during the 1st trimester of pregnancy. Based on radiation dosimetry provided in proposed ^{64}CU-Dotatate Injection labeling, the estimated mean radiation absorbed dose in the uterus in adult women who receive the recommended activity of 148 (b) (4) MBq (4 (b) (4) mCi) of ^{64}CU-Dotatate is (b) (4) mGy/MBq or (b) (4) mGy, which is below the estimated threshold of 100-200 mGy for fetal malformations caused by radiopharmaceuticals. However, the absorbed radiation dose would be higher in a fetus if placental transfer occurs with ^{64}CU-Dotatate. In this case, per the International Commission of Radiological Protection (ICRP),[20] the absorbed radiation dose to maternal organs and tissues may be representative of the absorbed dose to the corresponding fetal organs and tissues. Based on radiation dosimetry provided in proposed ^{64}CU-Dotatate Injection labeling, the kidneys (0.139 mGy/MBq or 20.6 10% mGy) are the organs with the highest estimated mean radiation absorbed dose in patients who receive the recommended activity of 148 (b) (4) MBq (4 (b) (4) mCi) of ^{64}CU-Dotatate. ^{64}CU-Dotatate Injection pregnancy labeling should include standard radiopharmaceutical product information that potential fetal harm is based on the radiation dose and the gestational timing of administration.

A postmarketing pregnancy safety study is not necessary for ^{64}CU-Dotatate as the potential fetal harm from all radiopharmaceuticals is based on the magnitude of the radiation dose and the gestational timing of radiation exposure.

Lactation

There are no lactation data available with the use of ^{64}CU-Dotatate. The radiation exposure to a breastfed infant comes internally, from the ingested radioactive breastmilk, and externally, from exposure to the mother who is a radiation source in close proximity to the infant during breastfeeding and normal infant care. Both of these factors should be considered when recommending the time, if any, is need to for a lactating women to interrupt breastfeeding. Breastfeeding after maternal administration of a radiopharmaceutical is considered to be safe when the maximum effective dose equivalent to a breastfed infant is less than 1 mSv (0.1 rem).[21] DMIRM is currently calculating the time it takes for the maximum effective dose equivalent to a breastfed infant after maternal administration of ^{64}CU-Dotatate Injection to be less than 1 mSv

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[17] ACOG Committee Opinion, Committee on Obstetric Practice: Guidelines for Diagnostic Imaging During Pregnancy and Lactation, Number 723; October 2017

[18] Refer to www.irpa net

[19] Refer to www.icrp.org Publication 106, Radiation Dose to Patients from Radiopharmaceuticals

[20] Refer to www.icrp.org Publication 84, Pregnancy and Medical Radiation

[21] Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, 6/26/2018, https://www.nrc.gov/docs/ML1817/ML18177A451.pdf

in order to provide the most accurate information for the period of time for a woman to interrupt breastfeeding. ^{64}CU-Dotatate radioactive decay is 127 hours or 5.3 days. During this time, a lactating woman may pump and store her breastmilk for use after the time for 10 half-lives of radiation decay has passed. ^{64}CU-Dotatate Injection lactation labeling should state the time that a lactating woman should avoid breastfeeding in order to limit radiation exposure to a breastfed infant.

A postmarketing lactation study is not recommended for ^{64}CU-Dotatate Injection due to rarity of neuroendocrine tumors, the high individual variability in breast radionuclide dose concentrations, and availability of lactation recommendations based on the isotope radioactive decay.

(b) (4)

LABELING RECOMMENDATIONS

DPMH revised Highlights of Prescribing Information, subsections 2.x, 8.1 and 8.2, and section 17 of ^{64}CU-Dotatate labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on May 27 and June 5, 2020. DPMH refers to the final NDA action for final labeling.

Reviewer comment: DMIRM is attempting to calculate the time it takes for the maximum effective dose equivalent to a breastfed infant after maternal administration of ^{64}CU-Dotatate Injection to be less than 1 mSv in order to provide the most accurate information for the period of time for a woman to interrupt breastfeeding. The time period to interrupt breastfeeding may be revised based to reflect the DMIRM calculations.

DPMH Proposed Pregnancy and Lactation Labeling

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise a lactating woman to avoid breastfeeding for 5 days after ^{64}CU-Dotatate Injection administration. (8.2)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.3 Patient Preparation

Pregnancy Status

Assessment of pregnancy status is recommended in females of reproductive potential before administering ^{64}CU-Dotatate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All radiopharmaceuticals, including ^{64}CU-Dotatate, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of radiation dose. Advise a pregnant woman of the potential risks of fetal exposure to radiation from administration of ^{64}CU-Dotatate Injection.

There are no available data on ^{64}CU-Dotatate Injection use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. . No animal reproduction studies have been conducted with ^{64}CU-Dotatate Injection.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of ^{64}CU-Dotatate in human milk, the effects on the breastfed infant, or the effects on milk production. Lactation studies have not been conducted in animals. Advise a lactating woman to avoid breastfeeding for 5 days after ^{64}CU-Dotatate administration in order to minimize radiation exposure to a breastfed infant,

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman of the potential risks of fetal exposure to radiation doses with ^{64}CU-Dotatate *[see Use in Specific Populations (8.1)]*.

Lactation

Advise a lactating woman to avoid breastfeeding for 5 days after administration in order to minimize radiation exposure to a breastfed infant *[see Use in Specific Populations (8.2)]*.

APPENDIX 1 – ACOG: Radiation Dose and Fetal Exposure[22]

Table 2. Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis ⇦

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after conception)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after conception)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	**Effects**	**Estimated Threshold Dose***
8–15 weeks	Severe intellectual disability (high risk)†	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).

†Because this is a period of rapid neuronal development and migration.

Reprinted from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 2007;27:1705–22.

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations ⇦

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Head or neck CT	1.0–10
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}F PET/CT whole-body scintigraphy	10–50

Abbreviations: CT, computed tomography; PET, positron emission tomography.

*Fetal exposure varies with gestational age, maternal body habitus, and exact acquisition parameters.

Note: Annual average background radiation = 1.1–2.5 mGy, ^{18}F = 2-[fluorine-18]fluoro-2-deoxy-D-glucose.

Reprinted from Tremblay E, Therasse E, Thomassin-Naggara I, Trop I. Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation. Radiographics 2012;32:897–911.

[22] ACOG Committee Opinion, Committee on Obstetric Practice: Guidelines for Diagnostic Imaging During Pregnancy and Lactation, Number 723; October 2017

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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:	May 18, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 213227
Product Name, Dosage Form, and Strength:	(b) (4) (Copper Cu 64 Dotatate) Injection, 148 MBq (4 mCi) per 4 mL at calibration (37 MBq (1 mCi) per 1 mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	RadioMedix Innovating Theranostics (RadioMedix Inc.)
FDA Received Date:	July 8, 2019, January 3, 2020, and February 27, 2020
OSE RCM #:	2019-1492
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

RadioMedix Innovating Theranostics submitted NDA 213227 (b) (4) (Copper Cu 64 Dotatate) injection on July 8, 2019 as part of a rolling review. (b) (4) is a radioactive diagnostic agent being proposed for positron emission tomography (PET) for (b) (4) localization (b) (4) of somatostatin receptor positive neuroendocrine tumors (NETs) in adults. We evaluated the proposed vial label, can carton labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

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 performed a risk assessment of the proposed Prescribing Information (PI), can carton labeling and vial label for (b) (4) to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation identified areas of vulnerability that may lead to medication errors. We note inconsistencies in strength statement between the vial and shield label.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed (b) (4) Prescribing Information (PI), can carton labeling, and vial label identified areas that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations for the Division in Section 4.1 and recommendations for RadioMedix Inc. in Section 4.2 below.

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

A. Highlights of Prescribing Information

1. The bullet containing the recommended dose contains (b) (4) We recommend the dose be described (b) (4) We also recommend revising the recommended dose to read to include the MBq listed first and mCi listed second in parenthesis as per normal practice. In addition, the dose should be the first bullet in this section.
2. We recommend removing (b) (4) as this information is not needed in this section (b) (4)
3. We recommend revising the last bullet to read "See Full Prescribing Information for preparation, administration, imaging and dosimetry information. (2)".
4. Revise Dosage Forms and Strengths statement to read "Injection: 148 MBq (4 mCi) per 4 mL at calibration (37 MBq (1 mCi) per 1 mL) of copper Cu 64 Dotatate Injection in single-dose vial. (3)".

B. Prescribing Information

1. Section 2: Dosage and Administration Section

   a. As currently presented, (b) (4) We recommended moving the information on pregnancy testing and patient instruction to a separate heading titled "Patient Preparation" in order to improve readability.

   b. We recommend revising the recommended dosage statement in Section 2.2 to include the route of administration as currently presented the route is not listed. In addition, the recommended dose contains (b) (4) We recommend the dose be described (b) (4) Additionally, present the megabecquerel (MBq) value first with the millicurie (mCi) equivalent in parenthesis.

   c. As currently presented, Section 2.4 only has a subheading for "Administration". We recommended including a subheading for "Preparation" for ease of readability.

d. We recommend including the statement "Calculate the necessary volume based on the calibration date and time" in Section 2.4 under the subheading preparation.

e. Include a statement in Section 2.4 under the subheading Administration instructions to read "Measure the patient dose immediately prior to administration in a dose calibrator".

f. [redacted] Revise [redacted]" to read [redacted]

g. In Section 2.4, the statement regarding the flush does not include the appropriate terminology per USP. Revise the statement to read "Follow the [redacted] with an intravenous flush of 0.9% Sodium Chloride Injection, USP to ensure full delivery of the dose."

2. Section 3: Dosage Forms and Strengths

a. Revise statement to read, "Injection: clear, colorless to yellow solution in a single-dose vial containing 148 MBq (4 mCi) per 4 mL (37 MBq (1 mCi) per mL) of copper Cu 64 Dotatate Injection at calibration time."

3. Section 16: How Supplied/Storage and Handling Section

a. Revise First statement to read "[redacted] (NDC 69945-064-01) is supplied as a clear, colorless to yellow injection in a [redacted] 10 mL single-dose vial containing 148 MBq (4 mCi) per 4 mL (37 MBq (1 mCi per mL) of copper Cu 64 Dotatate at calibration."

b. Revise Section 16 to include subheadings for Storage and for Handling. Appropriate information should be included under each subheading.

c. Provide the allowed temperature excursions from the proposed container labeling in the storage temperature requirements. On the proposed container labeling, the storage temperature is listed as 20° to 25°C (68° to 77°F). Place this information in the paragraph containing the information on storage in upright position.

d. Include a statement defining the expiration of the product. According to the label, [redacted] expires 2 hours after calibration. Include the statement, "Do not use and discard 2 hours after calibration".

e. We recommend adding proper handling and disposal instructions. Include the statement "This radiopharmaceutical is for distribution and use by persons licensed authorized by the U.S. Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State. Store and dispose of Copper Cu 64 Dotatate in compliance with the

appropriate regulations of the government agency authorized to license the use of this radionuclide."

4.2 RECOMMENDATIONS FOR RADIOMEDIX INNOVATING THERANOSTICS (RADIOMEDIX INC.)

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

A. Vial Container Label

1. As currently presented, the "Cu-" in the proposed proprietary name does not appear to be bolded like the rest of the letters of the name are. We recommend the entire proposed proprietary name be displayed in the same manner (i.e. boldness and font size) to prevent confusion.
2. The vial label and the can carton labeling use different packaging type terminology (b) (4) We recommend consistency in the package type terminology. In addition, consider revising the statement (b) (4) to read "Single-Dose Vial – Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.
3. We recommend revising storage requirements to read "Store at 20° to 25°C (68° to 77°F) upright in a lead shielded container" to prevent confusion.
4. Revise the strength statement (b) (4) Revise to read as follows:

   148 MBq (4 mCi) per 4 mL at calibration

   (37 MBq (1 mCi) per 1 mL)

5. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."
6. We recommend providing a location on the label where the expiration date/time can be imprinted on site before shipping. We recommend this being placed in close proximity to the calibration date/time and the statement "Expired 2 hours after calibration".

B. Can Carton Labeling

1. As currently presented, the "Cu-" in the proposed proprietary name does not appear to be bolded like the rest of the letters of the name are. We recommend the entire proposed proprietary name be displayed in the same manner (i.e. boldness and font size) to prevent confusion.

2. We recommend revising the statement [redacted] (b) (4) to read “Single-Dose Vial – Discard Unused Portion” to minimize risk of the entire contents of the vial being given as a single dose.

3. As currently presented, the contents statement reads with mCi listed first. Revise statement to read “Contains 37 MBq (1 mCi) per mL of copper Cu-64 dototate at calibration”.

4. Per 21 CFR 201.15(a)(6), the strength should be prominently displayed on the principal display panel (PDP). We recommend prominently displaying the total product strength on the principal display panel above the route statement. Revise to:

    148 MBq (4 mCi) per 4 mL at calibration

    (37 MBq (1 mCi) per 1 mL)

5. Increase prominence of the route of administration statement “For Intravenous Use Only”. Consider placing on its own line to prevent confusion.

6. We recommend revising storage requirements to read “Store at 20° to 25°C (68° to 77°F) upright in a lead shielded container” to prevent confusion.

7. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read “Recommended Dosage: See prescribing information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for [redacted] received on January 3, 2020 from RadioMedix Innovating Theranostics (RadioMedix Inc.).

Table 2. Relevant Product Information for [redacted]	
Initial Approval Date	N/A
Active Ingredient	Copper Cu 64 Dotatate
Indication	Indicated for use with positron emission tomography (PET) for [redacted] localization [redacted] of somatostatin receptor positive neuroendocrine tumors (NETs) in adults.
Route of Administration	Intravenous Injection
Dosage Form	Injection
Strength	148 MBq (4 mCi) per 4 mL at calibration (37 MBq (1 mCi) per 1 mL)
Dose and Frequency	148 MBq (4 mCi) administered as a single intravenous bolus injection.
How Supplied	Sterile, [redacted] clear, colorless to yellow solution [redacted] in a [redacted] 10 mL single-dose vial. [redacted]
Storage	[redacted]
Container Closure	[redacted]

APPENDIX G. LABELS AND LABELING

G.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 (b) (4) labels and labeling submitted by RadioMedix Innovating Theranostics (RadioMedix Inc.).

- Vial Container label received on January 3, 2020
- Carton labeling received on January 3, 2020
- Prescribing Information (Image not shown) received on January 3, 2020, available from \\cdsesub1\evsprod\nda213227\0006\m1\us\114-labeling\114a-draft-label\uspi.pdf

G.2 Label and Labeling Images

- **Vial Container Label**

(b) (4)

- **Carton Labeling**

(b) (4)

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

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