CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208870Orig1s000

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 15, 2017
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 208870
Product Name and Strength:	Kit for the Preparation of Technetium Tc99m Exametazime (b) (4)
Applicant/Sponsor Name:	Jubilant Draximage, Inc.
Submission Date:	August 14,2017
OSE RCM #:	2016-1660-03
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMO

The Division of Medical Imaging Products (DMIP) requested that we review the revised Carton and Container Labels for the Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (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.[abc]

[a] Rychlik, I. Label and Labeling Review for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (NDA 208870). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 22. RCM No.: 2016-1660.

[b] Rychlik, I. Label and Labeling Review for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (NDA 208870). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 29. RCM No.: 2016-1660.

[c] Rychlik, I. Label and Labeling Review for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (NDA 208870). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 10. RCM No.: 2016-1660

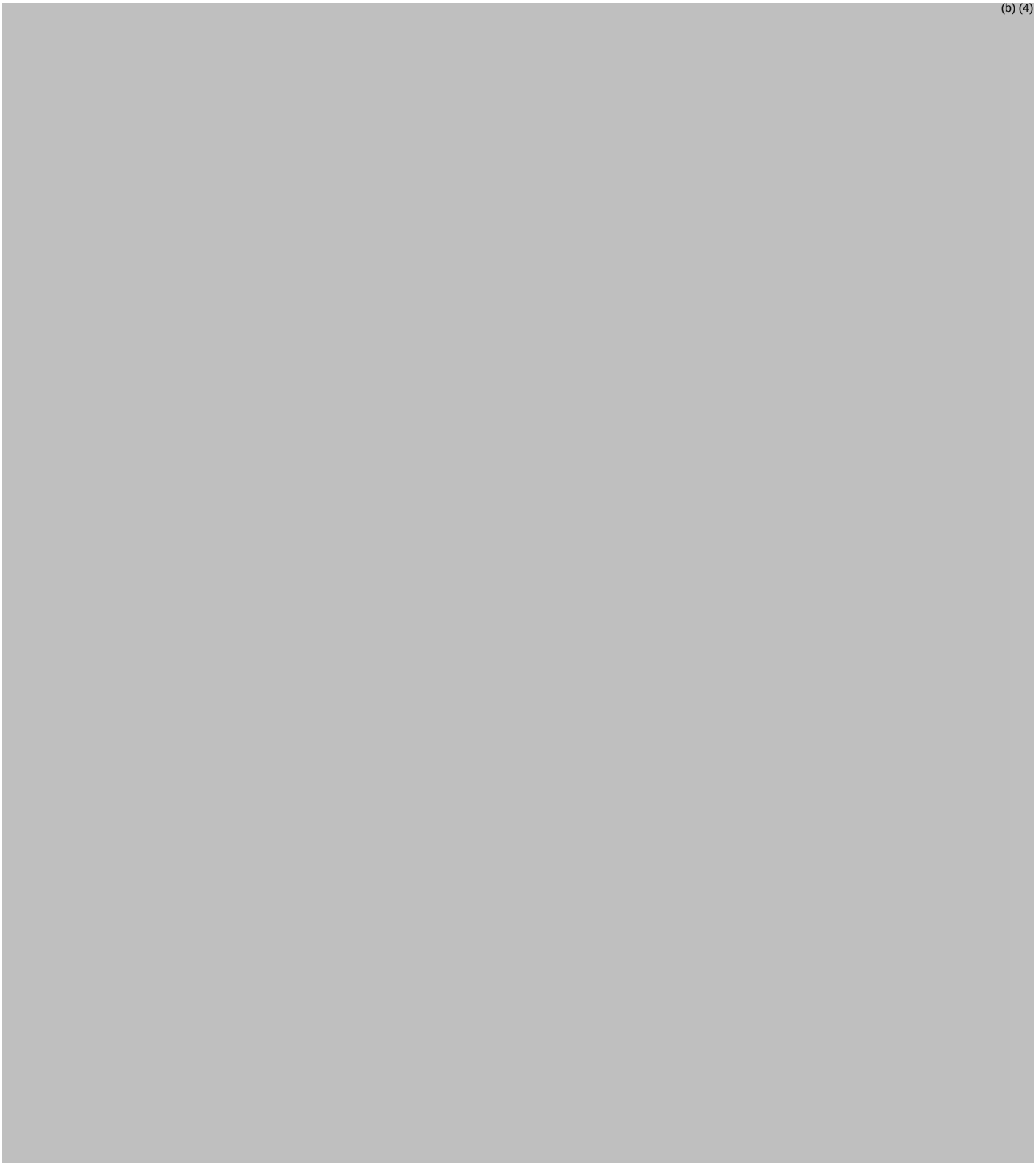
2 CONCLUSION

The revised carton and container labels for the Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) are acceptable from a medication error perspective. We have no further recommendations at this time.

A. APPENDIX A. LABEL AND LABELING SUBMITTED ON AUGUST 14, 2017

Container labels

(b) (4)



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/s/

IDALIA E RYCHLIK
08/15/2017

MISHALE P MISTRY on behalf of HINA S MEHTA
08/15/2017

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 11, 2017
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 208870
Product Name and Strength:	Kit for the Preparation of Technetium Tc99m Exametazime (b) (4)
Applicant/Sponsor Name:	Jubilant Draximage, Inc.
Submission Date:	August 4,2017
OSE RCM #:	2016-1660-02
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMO

The Division of Medical Imaging Products (DMIP) requested that we review the revised carton and container labels for the Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (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.[ab]

[a] Rychlik, I. Label and Labeling Review for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (NDA 208870). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 22. RCM No.: 2016-1660.

[b] Rychlik, I. Label and Labeling Review for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (NDA 208870). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 29. RCM No.: 2016-1660.

2 CONCLUSION

The revised carton and container labels for the Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) are unacceptable from a medication error perspective. Of note, the side image of the (b) (4) on carton labeling should align with the product's conditionally approved proprietary name in its entirety. The "Tradename" placeholder needs to be replaced with the conditionally approved Proprietary Name throughout all labels and labeling.

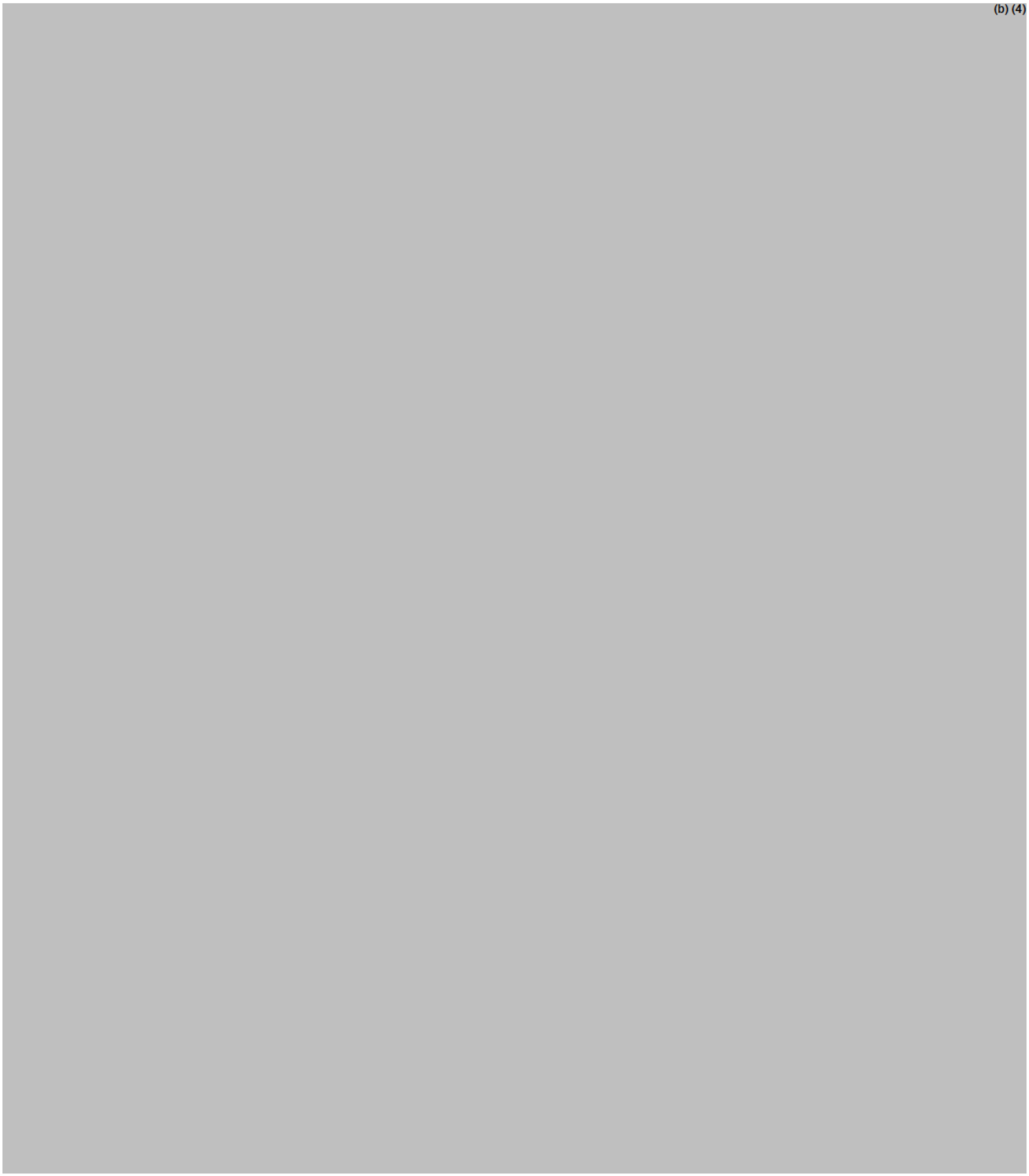
3 RECOMMENDATIONS FOR JUBILANT DRAXIMAGE, INC

We recommend the following be implemented prior to approval of this NDA 208870:

a. Replace the "Tradename" placeholder with the conditionally approved Proprietary Name on the carton labeling and container label.
b. The National Drug Code (NDC) number lacks identification as such on the container label, consider adding the denotation "NDC" before the numerical digits of the code.
c. To ensure that the National Drug Code (NDC) is not overlooked, we recommend relocating the NDC to the upper right hand corner on the container label. The "Rx Only" statement may be relocated.
d. The color logo on the side contains an image of the (b) (4) on the carton labeling. Please revise to align with the conditionally approved Proprietary Name in its entirety.

B. APPENDIX A. LABEL AND LABELING SUBMITTED ON AUGUST 4, 2017

Container labels



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/s/

IDALIA E RYCHLIK
08/11/2017

HINA S MEHTA
08/11/2017

DMIP Associate Director for Labeling Review of the Prescribing Information

Product Title	**Drax Exametazime (technetium exametazime for leukocyte labeling)**
Applicant	Draximage
Application/Supplement Number	208870
Type of Application/Submission	505(b)(2) New Drug Application (NDA)
Is Labeling Being Converted to PLLR?	Yes
Proposed Indication(s) (if applicable)	DRAX (b) (4) Exametazime is indicated (b) (4) for leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.
Approved Indication(s) (if applicable)	DRAX Exametazime is indicated for leukocyte (white blood cell) labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.
Date FDA Received Application	7/20/2016
Review Classification (Priority/Standard)	Standard
Action Goal Date	8/20/2017 (extended)
Review Date	7/25/2017
Reviewer	Michele B. Fedowitz

BACKGROUND

The sponsor is submitting a 505(b)(2) application for Tc 99m Exametazime indicated for leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease. The sponsor is relying on the reference listed drug, Ceretec (Kit for the preparation of Tc Exametazime (b) (4) The sponsor is not pursuing the second indication of the RLD: Tc99m exametazime scintigraphy may be useful as an adjunct in the detection of altered regional cerebral perfusion in stroke. The RLD is not in PLLR format, therefore, the sponsor is converting to PLLR.

This review includes a high-level summary of the rationale for major changes to the PI as compared to the applicant's draft PI.

Product Title (non-proprietary name)

Proposed: DRAX (b) (4) EXAMETAZIME (Kit for the Preparation of Technetium (Tc 99m) Exametazime (b) (4) for intravenous use.

FDA Proposed: DRAX EXAMETAZIME (kit for the preparation of technetium (Tc 99m) exametazime for leukocyte labeling) for intravenous use

Reviewer Comments: The Product title should include: Proprietary name, nonproprietary name (established name of the drug), dosage form, and Route of administration; 21 CFR 201.57(a)(2).

The approved proprietary name is DRAX EXAMETAZIME.

Technetium Tc 99m exametazime [redacted] *is the non-proprietary (established) name of the reference listed drug, Ceretec. The division suggested the non-proprietary name technetium (Tc 99m) exametazime for leukocyte labeling* [redacted]

DRAX Exametazime is a [redacted] *which is reconstituted with a sodium pertechnetate (Tc 99m) solution eluted from a generator to yield technetium Tc 99m exametazime solution. Autologous white blood cells (WBC) are then radiolabeled with the reconstituted solution. The Tc 99m exametazime labeled WBC are injected into the patient, not the reconstituted Tc 99m exametazime solution.* [redacted]

In the description for reconstitution, the reconstituted product is referred to as a solution throughout the labeling.

(1) Indication Statement

Proposed: DRAX [redacted] Exametazime is indicated [redacted] for leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.

FDA Proposed: Drax Exametazime is indicated for leukocyte (white blood cell) labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.

Reviewer Comments: This section was revised consistent with 21 CFR 201.57 (c)(2). [redacted] *Radiopharmaceutical imaging products are unique in that they are often used one time in a particular patient and are microdoses of the drug product.* [redacted]

(2) Dosage and Administration

Reviewer's Comments: The entire section was revised per 21 CFR 201.57 (c)(3) for clarity. Information that was repetitive within the section or within other parts of the label, or information that was practice of medicine was deleted. Information pertinent to other sections (8.3, 8.6, 11, and 16) was moved to the appropriate section. For example, moved storage and handling information into 16.

The reconstitution and radiolabeling instructions were ordered to conform to the order they would be performed. Specifically, the autologous WBC should be prepared before the product is reconstituted. The reconstituted solution must be used (for radiolabeling WBC) within 30 minutes. This expiration mandates that the WBC be prepared first, before the reconstitution of the Tc 99m exametazime solution. Therefore, the label was ordered this way for clarity to the end user.

2.9 Radiation Dosimetry

Reviewer's Comments: (b) (4) [redacted]

(3) Dosage Forms and Strengths
Reviewer's Comments: (b) (4) [redacted] *removed and information revised as per 21 CFR 201.57 (c)(4)*

(5) Warnings and Precautions
Reviewer's Comments: This section was revised to make information more concise. Specifically, information was removed from 5.2 Risk for Image Interpretation Error, (b) (4) [redacted].

(6) Adverse Reactions
Reviewer's Comments: Adverse Reactions are from the RLD (Ceretec) and were not altered.

(8) Use in Specific Populations
Reviewer's Comments: The entire section was revised to comply with PLLR. Section 8.2, Lactation, was further revised with respect to the duration of interruption of breast feeding after administration based on the administered activity.

Proposed:
Risk Summary
(b) (4) [redacted]

(b) (4) [redacted]

FDA Proposed:
Risk Summary
There are limited data available in the scientific literature on the presence of technetium Tc 99m exametazime in human milk. There no data available on the effects of technetium Tc 99m exametazime on the breastfed infant or the effects on milk production. Exposure of technetium Tc 99m exametazime to a breast fed infant can be minimized by temporary discontinuation of breastfeeding [*see Clinical Considerations*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for technetium Tc 99m exametazime, any

potential adverse effects on the breastfed child from technetium Tc 99m exametazime or from the underlying maternal condition.

Clinical Considerations
To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breast milk after the administration of technetium Tc 99m exametazime-labeled leukocytes for 12 to 24 hours, where the duration corresponds to the typical range of administered activity, 259 MBq to 925 MBq (7 mCi to 25 mCi).

Reviewer's Comments: The duration of interruption of breastfeeding was revised based on the US Nuclear Regulatory Commission (NRC) regulation and guidance. Please Refer to Dr Stanley Stern's review[1] for full details. Briefly, Section 8.2, Lactation, was revised based on the NRC regulation and guidance (NUREG-1556)[5]. The regulations require medical licensees to provide instructions to nuclear-medicine patients that would limit the total effective dose equivalent (TEDE) to a nursing infant or child to not more than 1 mSv. In developing guidance for such instructions, NRC assumed that the activity released into breast milk is in the form of pertechnetate ($^{99m}TcO_4^-$), and it modeled the biodistribution of the pertechnetate as following an intravenous administration. The interruption of breastfeeding was longer than that proposed by the sponsor and represents a more conservative approach and stronger radiation-protection safeguard based on the NRC regulations..

(11) Description
11.2 Physical Characteristics
Table 2 – Principal Radiation Emission data Tc 99m: Updated[6]
11.3 External Radiation
Exposure Rate Constant and Table 3 - Radiation Attenuation by Lead Shielding: Updated[7]

(14) Clinical Studies
Reviewer's Comments: Clinical Studies are from the RLD (Ceretec) and were, largely, not altered. Instances of passive voice and vague language ((b) (4)) were removed.

(16) How Supplied/Storage and Handling
Reviewer's Comments: Reordered per 21 CFR 201.57 (c)(17). NDC code added.

[1] Stanley Stern, PhD., Radiation Dosimetry Safety Report NDA 208870, 3/24/2017, DARRTS reference ID: 4074332

[2] ICRP Publication 128, *Radiation Dose from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances*, Approved by the International Commission on Radiological Protection in July 2014, *Annals of the ICRP*, Vol. 44, No. 2S, Sage Journals, 2015.

[3] M.L. Brown, J.C. Hung, R.J. Vetter, M.K. O'Connor, S. Chowdhury, and L.A. Forstrom, "The Radiation Dosimetry and Normal Value Study of 99mTc-HMPAO-Labeled Leukocytes," *Investigative Radiology*, Vol. 29, No. 4, pp. 443-447, April 1994.

[4] Peter D. Robins, Isabel Salazar, Lee A. Forstrom, Brian P. Mullan, and Joseph C. Hung, "Biodistribution and Radiation Dosimetry of Stabilized 99mTc-Exametazime-Labeled Leukocytes in Normal Subjects," *The Journal of Nuclear Medicine*, Vol. 41, No. 5, pp. 934-940, May 2000.

[5] D.B. Howe, M. Beardsley, and S. Bakhsh, *Consolidated Guidance About Materials Licenses. Program Specific Guidance About Medical Use Licenses*. Final Report, NUREG-1556 Vol. 9, Rev. 2, Appendix U- "Model Procedure for

Release of Patients or Human Research Subjects Administered Radioactive Materials," U.S. Nuclear Regulatory Commission, January 2008.

[6] C. Morillon, M.M. Bé, V. Chechev, A. Egorov, "$^{99}Tc^{m}$ – Comments on evaluation of decay data," Dec 2000, with half-life update Jan 2004, http://www.nucleide.org/DDEP_WG/Nuclides/Tc-99m_com.pdf, from *Recommended Data* of the *Table de Radionucléides*, Laboratoire National Henri Becquerel, Commissariat à l'Énergie Atomique (CEA), Saclay, France, http://www.nucleide.org/DDEP_WG/DDEPdata.htm, Oct 4, 2016.

[7] David S. Smith and Michael G. Stabin, "Exposure Rate Constants and Lead Shielding Values for Over 1,100 Radionuclides," *Health Physics*, Vol. 102, No. 3, pp. 271-291, March 2012.

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/s/

MICHELE B FEDOWITZ
07/25/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 208870	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Drax Exametazime Established/Proper Name: Kit for the Preparation of Tc99m Exametazime (b) (4) Dosage Form: Lyophilized (b) (4) Strengths: 0.37 GBq up to 2.00 GBq (10 mCi up to 54 mCi) at time of preparation (reconstitution)		
Applicant: Jubilant DraxImage Inc.		
Date of Receipt: July 20, 2016		
PDUFA Goal Date: August 20, 2017	Action Goal Date (if different): August 18, 2017	
RPM: Alberta Davis-Warren		
Proposed Indication(s): Indicated (b) (4) for leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 019829 Ceretec (technetium Tc-99m exametazime kit)	FDA's previous findings of safety/effectiveness (clinical and nonclinical)
Published literature	PI label sections: 2.5 Radiation Dosimetry 3 Dosage Forms and Strengths

	8.1 Pregnancy 8.2 Lactation 11.2 Physical Characteristics 11.3 External Radiation 12.3 Pharmacokinetics – Elimination

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The bridge is established per an in vitro equivalence study comparing the proposed product and Ceretec on two clinically relevant endpoints, % labeling efficiency and % cell efflux radioactivity. The product was shown to meet bioequivalence criteria on both endpoints. Furthermore, the proposed product and Ceretec have similar physio-chemical properties with respect to pH, osmolality, density, specific gravity, viscosity, lipophilicity, and enantiomeric excess. The proposed product has the same qualitative and quantitative formulation as Ceretec after reconstitution.

The relied upon literature describes information on radioactive diagnostic agents containing the same Tc99m radionuclide and Tc99m-labeled leukocytes which is directly applicable to the proposed product.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES X NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Ceretec

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES X NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Ceretec	019829	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application is seeking approval for one of the two indications for which the relied upon listed drug (Ceretec) is approved.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): NDA 019829

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 4789736

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

ALBERTA E DAVIS WARREN
08/14/2017

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:	July 6, 2017
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 208870
Product Name and Strength:	Kit for the Preparation of Technetium Tc99m Exametazime (b) (4)
Applicant/Sponsor Name:	Jubilant Draximage, Inc.
Submission Date:	June 29, 2017
OSE RCM #:	2016-1660-01
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMO

The Division of Medical Imaging Products (DMIP) requested that we review the revised Prescribing Information (PI), leukocyte labeling schematic, Carton and Container Labels for the Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (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 PI and carton labeling for the Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) are acceptable from a medication error perspective. However, the revised container label is unacceptable from a medication error perspective. The addition of

[a] Rychlik, I. Label and Labeling Review for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) (NDA 208870). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 22. RCM No.: 2016-1660.

(b) (4), reduces the readability and prominence of important administration directions (e.g. route of administration).

3 RECOMMENDATIONS FOR JUBILANT DRAXIMAGE, INC

We recommend the following be implemented prior to approval of this NDA 208870:

A. Increase the prominence of the route of administration statement as currently presented this important information is difficult to read.
B. Relocate the (b) (4) to increase readability of other important information.
C. Consider reorienting the barcode to a vertical position to improve scan-ability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[b]

[b] Neuenschwander M. et al. Practical guide to bar coding for patient medication sfety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

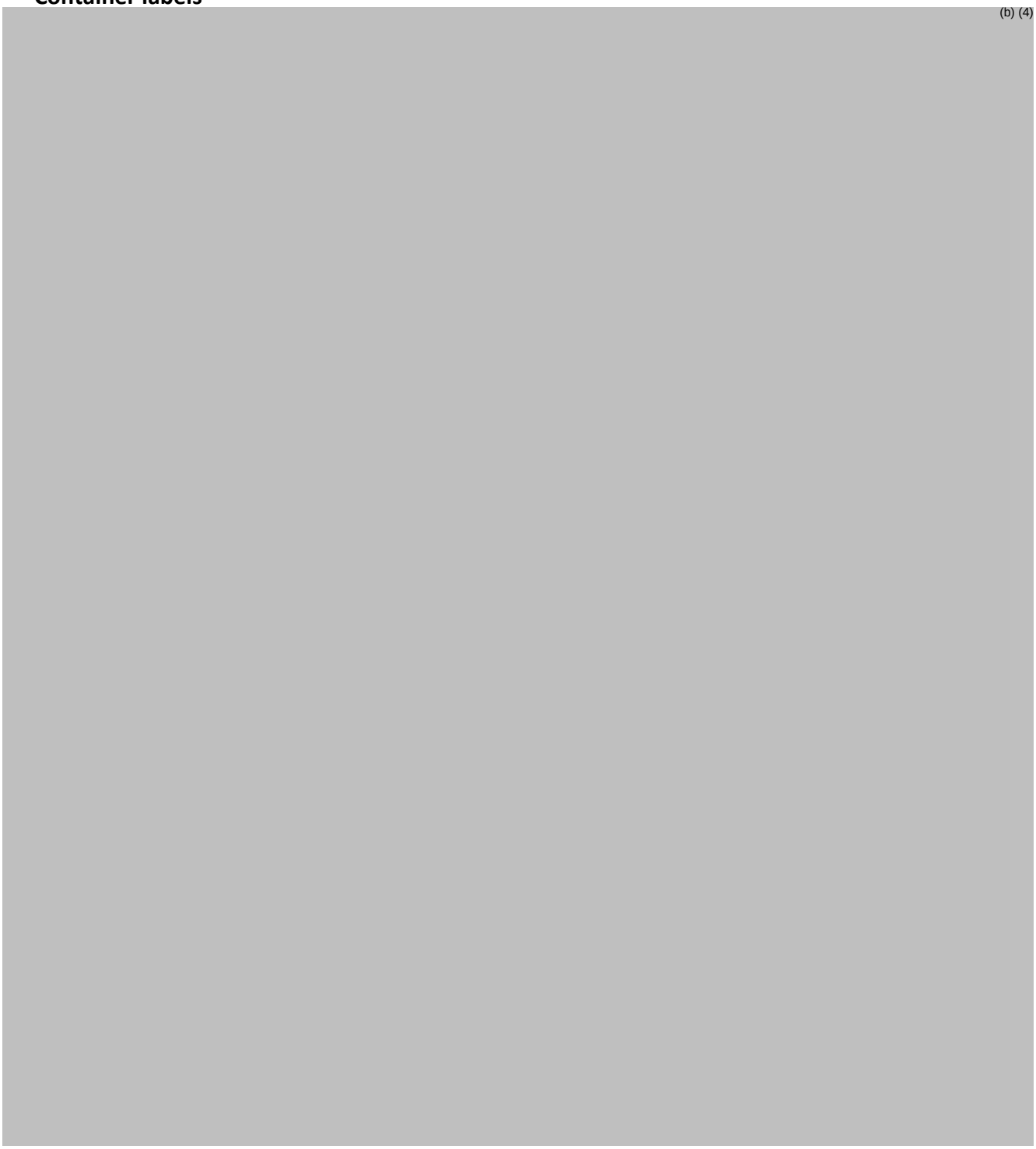
APPENDIX A. LABEL AND LABELING SUBMITTED ON JUNE 29, 2017

\\cdsesub1\evsprod\nda208870\0025\m1\us\114-labeling\114a-draft-label\pi-exametazime-clean.docx

\\cdsesub1\evsprod\nda208870\0025\m1\us\114-labeling\114a-draft-label\radiolabeled-leucocytes-lead-pot-labels.pdf

Container labels

(b) (4)



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/s/

IDALIA E RYCHLIK
07/06/2017

HINA S MEHTA
07/07/2017

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
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: March 29, 2017 **Date consulted:** July 25, 2016

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Ethan Hausman., MD, Medical Officer, Pediatrics
Division of Pediatric and Maternal Health

Hari Sachs, M.D., Team Leader, Pediatrics
Division of Pediatric and Maternal Health

Jane Liedtka, M.D., Acting 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 Products (DMIP)

Drug: Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4)

NDA: 208870

Applicant: Jubilant DraxImage

Subject: Pregnancy and Lactation Labeling

Indication: For leukocyte labeled scintigraphy as an adjunct in the localization of (b) (4)

Materials Reviewed:

- July 20, 2016, applicants submitted background package for NDA 208870
- July 25, 2016, DMIP consult to DPMH, DARRTS reference ID 3963565

Consult Question: Please review the package insert, specifically sections 8.1 Pregnancy, 8.2 Lactation and 8.4 Pediatric Use

INTRODUCTION

DMIP consulted the Division of Pediatric and Maternal Health (DPMH) to review subsections 8.1 Pregnancy, 8.2 Lactation and 8.4 Pediatrics for the Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) package insert.

REGULATORY HISTORY

On July 20, 2016, Jubilant DraxImagine, Inc., submitted a New Drug Application (208870) for the Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) for leukocytes labeled scintigraphy as an adjunct in the localization of (b) (4) intra-abdominal infection, inflammatory bowel disease. (b) (4) NDA 208870 is a 505(b)(2) application relying on the safety and efficacy of the reference listed drug, Ceretec (Technetium TC-99M Exametazime Kit) NDA 019829. The proposed drug product and the reference listed drug are chemically and pharmaceutically equivalent. Both drug products have the same formulation, strength, dosage form and route of administration; however, NDA 208870 is only seeking approval for one of the two approved Ceretec indications (b) (4)

- Ceretec, NDA 019829, was originally approved on December 30, 1988, as a diagnostic radiopharmaceutical for use as adjunct in the detection of altered regional cerebral perfusion in stroke.
  - The indication was updated on August 5, 2013, to also include, "for leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease."

BACKGROUND

Drug Characteristics[1,2]

Currently, 21 isotopes of technetium have been discovered from ^{90}Tc to ^{110}Tc. The activity moiety for Tc99m exametazime is formed when (b) (4)

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.03 hours. Tc99m leukocyte activity is seen during the first hour of injection in the lungs, liver, spleen, blood pool, bone marrow and the bladder. The kidneys and gall bladder may also be visible. The bowel is visible over the first 1-6 hours. Colonic activity is seen 24 hours post-injection. Adverse reactions that have been seen after exposure to technetium Tc99m exametazime include rash with generalized erythema, facial edema, fever (in less than 1% of patients), and a transient increase in blood pressure (8% of patients).

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[1] Reference listed drug labeling. 8/5/2013. Ceretec (Kit for the Preparation of Technetium Tc99m Exametazime) (b) (4)

Kowalsky, R., (2006). Technetium Radiopharmaceutical Chemistry. UNM College of Pharmacy.

Radiation Units and Conversions[3]

According to the Department of Health and Human Services, Radiation Emergency Medical Management, the following tables can be used for radiation units and conversions.

International System of Units (SI) and Common Unit Terminology[3]

	SI Units*	Common Units
Radioactivity	becquerel (Bq)	curie (Ci)
Absorbed Dose	gray (Gy)	rad
Dose Equivalent	sievert (Sv)	rem
Exposure	coulomb/kilogram (C/kg)	roentgen (R)

* SI Units: International System of Units

Note: In the table above the common units and SI units in each row are not equivalent in value, i.e., 1 curie does not equal 1 becquerel, but they both measure the same parameter.

Conversion Equivalence[3]

1 curie	=	3.7 x 10^{10} disintegrations per second
1 becquerel	=	1 disintegration per second
1 millicurie (mCi)	=	37 megabecquerels (MBq)
1 rad	=	0.01 gray (Gy)
1 rem	=	0.01 sievert (Sv)
1 roentgen (R)	=	0.000258 coulomb/ kilogram (C/kg)
1 megabecquerel (MBq)	=	0.027 millicuries (mCi)
1 gray (Gy)	=	100 rad
1 sievert (Sv)	=	100 rem
1 coulomb/ kilogram (C/kg)	=	3,880 roentgens

[3] Radiation Units and Conversion. Department of Health and Human Services. Radiation Emergency Medical Management. https://www.remm.nlm.gov/radmeasurement htm. Accessed 27 March 2017.

Radiation Exposure and Pregnancy[4,5,6,7,8]

According to the International Commission on Radiological Protection (ICRP), the American College of Radiology (ACR) and the American Congress of Obstetrics and Gynecologists (ACOG), most routine diagnostic imaging exams result in exposures much lower than 50-100 mGy. Fetal exposure to radiation at levels below 50-100 mGy should not warrant a terminated pregnancy. Doses above 100 mGy are associated with a rate of 1% risk of organ malformation and an increased risk of the development of childhood cancers. Between 8 to 15 weeks gestation the fetus is most vulnerable to levels above 100 mGy with effects such as intrauterine growth retardation and CNS defects such as microcephaly and mental retardation.

The ACOG Guidelines[8], released in 2016, explain that imaging studies to evaluate acute and chronic conditions are sometimes necessary during pregnancy. Additionally, ACOG states the following:

- "Ultrasonography and magnetic resonance imaging (MRI) are not associated with risk and are the imaging techniques of choice for pregnant patient, but they should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patients.
- 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, or are more readily available for the diagnosis in question, they should not be withheld from the pregnant patient.
- The use of gadolinium contrast with MRI should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome."

Additionally, the risk to the fetus from exposure to ionizing radiation is dependent on the gestational age during exposure (see Table 2 below from the publication). Exposure to high doses (> 1 Gy, i.e., 1000 mGy) that occur during embryogenesis could likely be lethal to the embryo; however, doses this high are not often used for routine diagnostic imaging. The most common adverse events demonstrated after exposure to high doses of radiation are growth restriction, microcephaly and intellectual disability. It is suggested that intellectual disability has been shown at exposures that occur during 8 to 15 weeks gestation, in the range of 60 to 310 mGy. However, multiple diagnostic x-ray procedures rarely result in ionizing radiation exposure this high. (See Table 3 below from the publication for fetal radiation doses associated with common radiologic exams.) Fetal anomalies, growth restriction or abortion have not been reported in radiation exposure of < 50 mGy, which is a level above the range of exposure for

[4] Wang P, *et al.* (2012). Imaging of Pregnant and Lactating Patients: Part 1, Evidence-Based Review and Recommendations. *AJR*, 778-783.
[5] American College of Radiology (ACR) Practice Guidelines (2008). Pregnant or Potentially Pregnant patients, (26), 23-37.
[6] J. Valentin (2000). Annals of the ICRP: Pregnancy and Medical Radiation. *International Commission on Radiological Protection (ICRP)*, SE 171 16 Stockholm, Sweden.
[7] ICRP Addendum 3 to ICRP Publication 53. Annals of the ICRP. Radiation Dose to Patients from Radiopharmaceuticals, 106, 3-197.
[8] Committee on Obstetric Practice, ACOG. (2016). Guidelines for Diagnostic Imaging During Pregnancy, number 656.

diagnostic procedures. The risk of carcinogenesis after *in utero* exposure to ionizing radiation is unclear.

ACOG – Effects of Radiation Dose at Various Stages of Organogenesis[8]

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.

ACOG – Fetal Radiation Doses with Common Radiologic Exams[8]

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.

Current State of the Labeling for the Reference Listed Drug

The reference listed drug, Ceretec, is not in the PLR/PLLR format. There is no boxed warning for embryofetal toxicity. The current pregnancy, lactation and pediatric subsections are found under the Precautions sections, under the subheading Pregnancy, Nursing Mothers and Pediatrics. The following language is found in those subsections:

Pregnancy

Animal reproduction studies have not been conducted with Tc99m exametazime. It is also not known whether Tc99m exametazime can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity. Therefore, Tc99m exametazime should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Technetium Tc99m is excreted in human milk during lactation. It is not known whether exametazime is excreted in human milk. Therefore, formula feedings should be substituted for breast feeding for 60 hours.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[9] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[10] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience

Animal reproduction studies have not been performed.

Applicant's Review of the Literature

The applicant performed a review of the published literature using PubMed without any Restriction on the time period and using the following keywords: [(exametazime or exametazine or hexamethyl or hm-pao) and (technetium or 99m)) or Ceretec) and (pregnancy* or pregnant* or fetus* or fetal* or placenta*)]. Sixteen publications were identified from which four were

[9] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[10] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

determined to be relevant. Additionally, the applicant provided guidelines on nuclear medicine and on the use of radiopharmaceuticals in pregnant and lactating women. The submitted publications and guidelines are reviewed below.

Guidelines on Radiopharmaceuticals and Pregnant Women
American College of Radiology (ACR)
The American College of Radiology (ACR)[5] guidelines for imaging of pregnant females and females of reproductive potential were developed to address the imaging of pregnant and possibly pregnant females who may be exposed to x-rays (planar radiography, fluoroscopy and computer tomography). The guidelines do not address the issues of nuclear medicine, lactation or safety issues regarding the use of iodinated contrast or gadolinium contrast imaging or those patients who may undergo radiation treatment or pregnant medical personnel working with ionizing radiation.

Thousands of females are exposed to ionizing radiation each year from diagnostic imagining many of those are unintentionally exposed when they were unknowingly pregnant. The majority of diagnostic routine testing delivers less than 20mGy to the uterus and computer tomography (CT) of the abdomen and pelvis deliver less than 35mGy. The ACR has developed the following tool (see table[5] below) to aid in the development of policies and procedures in the clinical management of pregnant or potentially pregnant patients.

Table 1: Summary of Suspected In-Utero Induced Deterministic Radiation Effects* [3,4]

Menstrual or Gestational age	Conception age	<50 mGy (<5 rad)	50-100 mGy (5 - 10 rad)	>100 mGy (>10 rad)
0 - 2 weeks (0 - 14 days)	Prior to conception	None	None	None
3rd and 4th weeks (15 - 28 days)	1st - 2nd weeks (1 - 14 days)	None	Probably none	Possible spontaneous abortion.
5th - 10th weeks (29 - 70 days)	3rd - 8th weeks (15 - 56 days)	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable.	Possible malformations increasing in likelihood as dose increases.
11th - 17th weeks (71-119 days)	9th - 15th weeks (57 - 105 days)	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable.	Increased risk of deficits in IQ or mental retardation that increase in frequency and severity with increasing dose.
18th - 27th weeks (120 - 189 days)	16th - 25th weeks (106 - 175 days)	None	None	IQ deficits not detectable at diagnostic doses.
>27 weeks (>189 days)	>25 weeks (>175 days)	None	None	None applicable to diagnostic medicine.

International Commission on Radiological Protection (ICRP)[6,7]

The purpose of these guidelines is to cover the issues of pregnancy and the exposure of ionizing radiation, including the exposure of pregnant workers and to provide a practical approach that can be instituted in a variety of settings. According to the ICRP, the central nervous system is sensitive to radiation during a period of 8 to 25 weeks post conception and fetal doses in the rage of 1,000mGy (1Gy) can result in severe mental retardation and low IQ. In addition, radiation has been demonstrated to cause leukemia and many types of cancers in adults and children. The ICRP assumes this risk is equal in the embryo/fetus. Preconception irradiation of male/female gonads has not demonstrated an increased risk of cancers or malformations in the offspring. See Appendix B for an approximate fetal dose from common diagnostic procedures from the ICRP. The ICRP summarizes that medical professionals ought to be familiar with the risk of radiation exposure to the embryo/fetus and that exposures in excess of 100-200 mGy can lead to nervous system abnormalities, malformations, childhood cancers, growth retardation and fetal death. Additionally, prior to exposure females should be evaluated for pregnancy. An informed consent should be given based on individual circumstances and termination of pregnancy at fetal exposure of less than 100 mGy is not justified.

Table 1:[11] ***Case Reports of Exposures to Technetium during Pregnancy***

Publication	Subject	Exposure	Outcome	Conclusion
Kume (1997)[12]	19 year old female with Moyamoya disease	Technetium-99m-HMPAO brain SPECT (333MBq) with hyperventilation challenge to examine cerebral blood flow and vascular reserve at 27 weeks gestation	Healthy infant delivered at 38 weeks gestation with Apgar score of 8 (1 min), 9 (5 min) and 9 (10min)	Authors concluded that a small dose of radiation has a negligible risk to the fetus
Maguire (1990)[13]	30 year old female with subarachnoid hemorrhage due to rupture of a basilar artery aneurysm	Exposure occurred while patient was in a deep coma and 32 weeks pregnant using Technetium 99m-HMPAO, dose not specified	Infant was delivered by cesarean section. Infant also received imaging using gamma camera several hours after birth to determine location of Technetium 99m-HMPAO which was observed in the fetal liver with lesser	Authors hypothesized that Technetium 99m crossed the placenta and was taken up in the fetal liver with smaller amounts in the abdomen likely due to biliary excretion

[11] Table created by DPMH Reviewer. C. Ceresa.

[12] Kume N, *et al*. (1997). Hyperventilation Technetium-99m-HMPAO Brain SPECT in Moyamoya Disease to Assess Risk of Natural Childbirth. *The Journal of Nuclear Medicine*, 38(12), 1894-1897.

[13] Maguire C, *et al.* (1990). Hepatic Uptake of Technicium-99m HM-PAO in a Fetus. *The Journal of Nuclear Medicine*, 31, 237-239.

Publication	Subject	Exposure	Outcome	Conclusion
			amounts in the abdomen, there were no significant cerebral concentrations	

A retrospective chart review by Stewart *et al* (2006)[14], evaluated all pregnant patients who underwent a nuclear medicine exam due to appendicitis at a single community hospital from 1999 through 2005. A total of 13 patients were included in the final analysis from age 16 to 36. All patients were exposed to Technitium-99m at levels not reported. Two patients delivered healthy infants at term; however, the outcomes of the remaining patients were not reported.

DPMH review of literature

DPMH conducted a search of published literature in PubMed using the search terms "technetium 99m and pregnancy," "Tc-99m and pregnancy," "technetium 99m and birth defects," "Tc-99m and birth defects," "technetium 99m and spontaneous abortion," "Tc-99m and spontaneous abortion." A review of published literature found in addition to that provided in the applicant's submission is found below. Additionally, the ACOG 2016 guidelines are summarized above in the Radiation Exposure during Pregnancy section of this review.

Prospective Observational Cohort Study[15]

A prospective observational cohort study was performed using data collected between 1991 and 2008 by the Berlin Institute for Clinical Teratology. Pregnancy outcomes of pregnant women exposed to technetium 99m scintigraphy of thyroid (n=102) or bone (n=20) were compared to a control group without exposure (n=366). The first table[15] below depicts estimated fetal doses by common procedures and the second table[15] displays fetal thyroid dose of Tc-99m pertechnetate.

Table 1
Energy dose to the embryo of diagnostical procedures with radiopharmaceuticals [7].

Organ or method	Radionuclide	Radiopharmaceutical	Dose coefficient (μGy/MBq)	Applied activity (MBq)	Energy dose (embryo/fetus) mGy
Bone	Tc-99m	MDP, HDP	6.1	750	4.6
Thyroid	Tc-99m	Pertechnetate	11	75	0.8
Kidneys	Tc-99m	DTPA	12	150	1.8
Kidneys	Tc-99m	MAG3	18	200	3.6
Lung	Tc-99m	Mikrospheres	2.8	200	0.6

Dose coefficient = the relation between applied activity and energy dose in the embryo. Largest values for early pregnancy were taken, according to Russell et al. [7].
Gy = Gray; energy dose of ionizing radiation absorbed by a body (1 Gy = 100 rad = 1 J/kg).
MBq = Mega-Becquerel; 1 Bq = 1 decay/s.
Applied activity = mean "dose" used for scintigraphy.

Table 2
Fetal thyroid dose after thyroid scintigraphy with Tc-99m pertechnetate at different gestational stages [23].

Method	Radiopharmaceutical	Applied activity (MBq)	Fetal thyroid dose (mGy)		
			95 days	130 days	250 days
Thyroid-scintigraphy	Tc-99m pertechnetate	75	0.7	1.7	0.6

Applied activity = mean "dose" used for scintigraphy.
MBq = Mega-Becquerel; 1 Bq = 1 decay/s.
Gy = Gray; energy dose of ionizing radiation absorbed by a body (1 Gy = 100 rad = 1 J/kg).

[14] Stewart D, *et al*. (2006). The use of tagged white blood cell scans to diagnose appendicitis in pregnant patients. *The American Surgeon*, 72, 894-896.
[15] Schaefer C, *et al*. (2009). Fetal outcome after technetium scintigraphy in early pregnancy. *Reproductive Toxicology*, 28, 161-166.

The tables[15] below display pregnancy outcome and the cumulative incidence of spontaneous abortions, elective terminations and live birth by percentage.

Table 4
Pregnancy outcome.

	Tc-99m, total	Tc-99m, bones	Tc-99m, thyroid	Controls
Exposed pregnancies	122	20	102	366
ETOPs	6/122	2/20	4/102	7/366
Spontaneous abortions (ETOPs excluded)	11/116	3/18	8/98	37/359
Live births	105	15	90	322[a]
Preterm births (<37 week)	4/105 (3.8)	0/15 (0.0)	4/90 (4.4)	30/322 (9.3)
All BD	9/108[b] (8.3)	1/16 (6.3)	8/92[b] (8.7)	28/323[c] (8.7)
Major BD[d]	4/108[e] (3.7)	1/16 (6.3)	3/92[e] (3.3)	12/323 (3.7)
All BD (1st trimester exposure only)	7/105[b] (6.7)	1/16 (6.3)	6/89[b] (6.7)	28/323[c] (8.7)
Major BD[d] (1st trimester exposure only)	3/105[e] (2.9)	1/16 (6.3)	2/89[e] (2.2)	12/323 (3.7)

( ) = percentages; BD = birth defects; ETOP = elective termination of pregnancy.
[a] 4 twins and 1 triplet (328 newborn).
[b] 1 major + 1 minor BD with ETOP plus 1 major BD with spontaneous abortion.
[c] Incl. 1 minor BD with ETOP.
[d] Genetic and chromosomal disorders excluded.
[e] 1 major BD with ETOP plus 1 major BD with spontaneous abortion.

Table 5
Cumulative incidences of spontaneous abortions, ETOPs and live births in percent.

	Tc-99m, total	Tc-99m, bones	Tc-99m, thyroid	Controls
Spontaneous abortions	12 (4)	17 (9)	11 (4)	21 (6)
ETOPs	6 (3)	12 (8)	4 (3)	2 (1)
Live births	82 (2)	71 (6)	85 (2)	76 (1)

ETOP = elective termination of pregnancy; ( ) = standard deviation.

The exposed group of mothers was older than the control group mothers. In addition, there were more cigarette smokers in the exposed group. The miscarriage rate was within normal range and the differences between the groups were not significant.

Major birth defects in pregnant women exposed to Tc-99m in this study included right ear dysplastic helix, atresia of external ear canal possibly in combination with anomaly of middle ear, exencephaly both brain sides, aortic stenosis, spina bifida. Minor birth defects include slight hip deformity, dilation of calix, umbilical hernia, hemangiomas. Concomitant medications include metoclopramide, omeprazole, hormonal birth control, clotrimazole, thyroxine, fenoterol, terfenadine, levocetirizine, betamethasone, citalopram, carbimazole, metoclopramide, clindamycin, and roxithromycin. The majority of patients were exposed in the first trimester (only 3 exposed 2nd trimester) therefore the authors conclude that it is difficult to make a conclusion with regard to Tc-99m exposure during the 2nd or 3rd trimesters. Additionally, the authors conclude that the study suggests that exposure to Tc-99m is early pregnancy is relatively safe.

Case Report[16]
A 35 year-old pregnant female (6 months gestation) with hematemesis and dark blood in stool was exposed to Tc-99m while being evaluated to determine an active gastrointestinal bleeding site. The evaluation results showed activity in the fetus and a large arteriovenous malformation in the patient. According to the publication, radiation dose is dependent on gestational age and a Tc-99m RBC *in vitro* scan administered at 20 mCi, equals a dose of 20 mGy to the fetus before 3 months gestation, 2.52 mGy at 6 months gestation and 2.07 mGy at 9 months gestation. The patient described in the publication received an intravenous injection of 20.3 mCi (751 MBq) of Tc-99m labeled RBC.

Review of Pharmacovigilance Database
Jubilant Draximage Inc. does not have any individual safety reports related to Technetium Tc-99m exametazime in its safety database. There is no safety data from post-marketing surveillance as this product NDA is not approved for marketing in any country.

Summary
The findings from the available data found in published literature with technetium Tc-99m exametazime and use in pregnant women are insufficient to inform a drug associated risk for major birth defects and miscarriage. Limited published literature describes Tc-99m exametazime crossing the placental barrier and visualization of radioactivity in the fetal liver. 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.

LACTATION
Nonclinical Experience
There is no nonclinical data with regard to Tc-99m exametazime and lactation.

Review of Applicant's Literature
The applicant performed a review of the published literature using PubMed without any restriction on the time period and using the following keywords: [(exametazime or exametazine or hexamethyl or hm-pao) and (technetium or 99m)) or Ceretec) and (lactation* or lactating* or (breast and feeding))]. Additionally, the applicant provided guidelines on nuclear medicine and on the use of radiopharmaceuticals in lactating women. The submitted publications and guidelines are reviewed below.

Guidelines on Radiopharmaceuticals and Lactation[7]
According to the ICRP, some radiopharmaceuticals administered to breastfeeding women may be excreted in the breast milk and transferred to the breast fed infant and consideration should be made to postpone procedures when possible. If the procedure is performed the infant should not be breast fed until the radiopharmaceutical is longer excreted in an amount estimated to give an effective dose > 1 mSv to the infant.

[16] Bural G, *et al*. (2011). Tc-99m Red Blood Cell Bleeding Scan in a Pregnant Woman Presenting With Hematemesis: A Brief Review of Indications and Guidelines for Radionuclide Scans During Pregnancy, *Clin Nucl Med*, 36, 987-990.

Case Report[17]

According to Marshall *et al*. (1996), the amount of radioactivity in breastmilk following a brain perfusion study using 500 MBq Tc99m-HMPAO was calculated to be 0.26 mSv administered to the infant. The authors concluded that an interruption in breast feeding is not essential; however, a short interruption should be considered to keep the dose to the infant as low as possible.

Observational Study[18]

Radioactivity was measured in the breastmilk from 53 breastfeeding patients. Milk collections were performed at various time points using 16 different radiopharmaceuticals. Estimations were made for the absorbed dose to the various organs and tissues and the effective dose to the infant (see Table 2 below from publication). A total of nine Tc-99m labelled radiopharmaceuticals were given to 35 breastfeeding mothers for this study. For Tc-99m, the total fraction of the administered activity in milk varies from 0.0057% for labeled red blood cells to 19% for Tc-99m pertechnetate. The effective dose to an infant per unit activity administered to the mother ranged from 6.7 × 10−6 mSv/MBq for 99mTc-labelled RBC to 3.6× 10−2 mSv/MBq for 99mTc-pertechnetate. The authors concluded that all breast milk should be expressed at least three times in a 12 hour period after exposure and discarded.

Table 2 Effective half-times of the various radiopharmaceuticals, total fractions excreted in the breast milk, effective doses to the newborn infant, and recommendations on breastfeeding interruption

Radiopharmaceutical	Effective half-time (h)	Total fraction excreted in breast milk (% injected activity)	Effective dose to the newborn infant ($mSv_{infant}/MBq_{mother}$)	Breastfeeding interruption
^{99m}Tc-labelled compounds				
DTPA	3.5 (3.2 – 3.8)	0.012 (0.010 – 0.014)	2.2×10^{-5} (1.8×10^{-5} – 2.7×10^{-5})	No
HMPAO-leucocytes	7.5	0.11	2.0×10^{-4}	No
MAA	4.0 (3.5 – 4.7)	3.7 (0.51 – 8.5)	7.0×10^{-3} (9.7×10^{-4} – 1.6×10^{-2})	Yes (12 h)
MAG3	4.2 (3.6 – 4.9)	0.073 (0.020 – 0.10)	1.4×10^{-4} (3.8×10^{-5} – 1.9×10^{-4})	No
MDP (blocked)	4.9 (4.6 – 5.2)	0.010 (0.0084 – 0.011)	1.2×10^{-5} (9.9×10^{-6} – 1.3×10^{-5})	No
MDP (not blocked)	3.6	0.027	5.2×10^{-5}	No
MIBI	5.4 (5.2 – 5.6)	0.048 (0.039 – 0.056)	9.0×10^{-5} (7.3×10^{-5} – 1.1×10^{-4})	No
Pertechnetate (not blocked)	3.4 (2.7 – 3.9)	10 (5.3 – 19)	1.9×10^{-2} (9.9×10^{-3} – 3.6×10^{-2})	Yes (12 h)
Pertechnetate (blocked)	5.2 (4.5 – 5.9)	0.82 (0.68 – 0.95)	9.6×10^{-4} (8.0×10^{-4} – 1.1×10^{-3})	Yes (12 h)
RBC (in vivo)	6.7	0.0057	6.7×10^{-6}	No
Tetrofosmin	4.8	0.082	1.5×10^{-4}	No
Other compounds				
^{14}C-GCA	143	9.2	6.9×10^{-1}	No
^{14}C-Triolein	15	14	4.1	No
^{18}F-FDG	1.8 (1.7 – 1.8)	0.070 (0.068 – 0.071)	6.7×10^{-4} (6.6×10^{-4} – 6.8×10^{-4})	No
^{51}Cr-EDTA	6.1 (4.9 – 7.2)	0.065 (0.018 – 0.11)	2.1×10^{-4} (5.6×10^{-5} – 3.5×10^{-4})	No
^{125}I-Iodohippurate	5.0	2.0	1.0	Yes (12 h)
^{131}I-Iodohippurate	6.3 (4.5 – 7.6)	2.4 (1.1 – 4.3)	5.3 (2.4 – 9.5)	Yes (12 h)
^{131}I-NaI	14 (10 – 17)	31 (13 – 48)	6.8×10^{1} (2.9×10^{1} – 1.1×10^{2})	Cessation

The data presented are means (range)

[17] Marshall *et al*. (1996). Measurement of the secretion of technetium-99m hexamethylpropylene amine oxime into breast milk. *Eur J Nucl Med*, 23, 1634-1635.

[18] Leide-Svegborn S *et al*. (2016). Excretion of radionuclides in human breast milk after nuclear medicine examinations. Biokinetic and dosimetric data and recommendations on breastfeeding interruption. *Eur J Nucl Med Mol Imaging*, 43, 808-821.

DPMH's Review of Literature

DPMH conducted a review of published literature using PubMed regarding Tc-99m and lactation. The following articles and clinical guidelines were reviewed.

Case Reports[11]

Publication	Patient	Maternal Exposure	Amount in milk	Conclusion
Mountford (1987)[19]	40 year old, breastfeeding established 6 months	100 MBq (2.7 mCi) $^{99}Tc^{M}$-perchnetate	5.2% of $^{99}Tc^{M}$-perchnetate and dose equivalent of 1.5 mSv	Interruption of breastfeeding for 12 hours recommended as by that time the dose exposure would be 0.2 mSv
	24 year old, breastfeeding 1 month	550 MBq (15 mCi) $^{99}Tc^{M}$-glucoheptonate	0.055% of $^{99}Tc^{M}$-glucoheptonate; dose equivalent not given	Interruption of breastfeeding not necessary but author recommends 4 hours to reassure mother

United States Nuclear Regulatory Commission (USNRC)[20]

The USNRC has established guidelines for breast feeding interruption after exposure to radiopharmaceuticals. These guidelines are based on 10CFR 35.75(b) which require a licensee to provide instructions on the discontinuation or the interruption period of breast-feeding and the consequence of failing to following the recommendation. See table in Appendix C for instructions from the USNRC for breastfeeding an infant or child when exposed to certain radiopharmaceuticals. According to the table, exposures to Tc-99m pertechnetate labeled white blood cells, of 1100 MBq (30 mCi) the duration of interruption for breastfeeding is 24 hours and for exposures of 440 MBq (12 mCi) the duration of interruption for breastfeeding is 12 hours. Additionally, if a radiopharmaceutical is not listed in that table it is recommended to "assume that 50% of the administered activity is excreted in the breast milk."

Reviewer comment: After discussions with DMIP, DPMH agreed to adapt the duration of interruption of breastfeeding recommendations from the USNRC. For a typical labeled dose of Tc-99m exametazime where exposure is 259 MBq to 925 MBq (7 mCi to 25 MCi) the recommended interruption of breastfeeding will include advising the female to pump and discard breast milk for 12 to 24 hours after administration.

[19] Mountford PJ *et al.* (1987). Breast milk radioactivity following injection of $^{99}Tc^{m}$-pertechnetate and $^{99}Tc^{m}$-glucoheptonate. *Nuclear Medicine Communications*, 8, 839-845.

[20] Model Procedure for Release of Patients or Human Research Subjects Administered Radioactive Materials. Appendix U. *United States Nuclear Regulatory Commission*. Volume 9. Revision 2. (2008)

National Library of Medicine (NLM) Drugs and Lactation Database (LactMed)[21]
According to LactMed, regarding Technetium Tc 99 m exametazime, breastfeeding does not need to be interrupted after administration of technetium Tc 99m exametazime in doses up to 500 MBq (15 mCi); however, often some experts recommend an interruption for 3 to 6 hours post dose by expressing milk and discarding. There is no information on the effects of Tc 99m exametazime on the breastfed infants or on the effects on lactation.

Summary
The applicant proposes a recommendation that women interrupt breastfeeding for (b) (4) hours post exposure. DPMH does not agree with this recommendation. DPMH, in agreement with DMIP, have agreed to adopt the USNRC guidelines found in the *Model Procedure for Release of Patients or Human Research Subjects Administered Radioactive Materials* to advise the mother to pump and discard breastmilk for 12 to 24 hours post exposure to a typical labeled dose of Tc-99m exametazime where exposure is 259 MBq to 925 MBq (7 mCi to 25 MCi).

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
There is no nonclinical information regarding technetium 99m exametazime and females and males of reproductive potential.

DPMH conducted a review of published literature in PubMed to evaluate the use of technetium 99m exametazime and its effects on fertility. There are no human or animal data available on the effects of technetium 99m exametazime on fertility to inform a potential clinical risk. In addition, pregnancy testing and contraception recommendations are not warranted; therefore, this subsection will be omitted from labeling.

CONCLUSIONS
The Pregnancy and Lactation subsections of the Kit for the Preparation of Technetium Tc 99m Exametazime labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," and "Clinical Considerations," sections."
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.2 of labeling.

[21] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provided information when available on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). In addition, because no new pediatric clinical data or animal toxicology data is submitted for section 8.4, DPMH – pediatrics recommends retaining the statement, "Safety and efficacy in pediatric patients have not been established", in accordance with language specified in 21CFR 201.57 in situations where pediatric data are absent. DPMH-pediatrics also recommends deleting the statement, (b) (4) No separate pediatric review will be performed. DPMH discussed our labeling recommendations with the division on February 7, 2017. DPMH recommendations are below and reflect the discussions with DMIP. DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant's proposed pregnancy and lactation labeling)

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Lactation: Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for 12 to 24 hours after Technetium Tc 99m Exametazime administration (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with technetium Tc-99m exametazime use in pregnant women are insufficient to inform a drug associated risk for major birth defects and miscarriage. Tc-99m exametazime is transferred across the placenta (*see Data)*. Animal reproduction studies with technetium Tc 99m exametazime have not been conducted. All radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering technetium Tc 99m exametazime administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from technetium Tc 99m exametazime and the gestational timing of exposure.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, 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 are 2-4% and 15-20%, respectively.

Data

Human Data

Limited published literature describes Tc-99m exametazime crossing the placental barrier and visualization of radioactivity in the fetal liver. 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.

8.2 Lactation

Risk Summary

There are limited data available in the scientific literature on the presence of Tc-99m exametazime in human milk. There no data available on the effects of Tc-99m exametazime on the breastfed infant or the effects on milk production. Exposure of Tc 99m exametazine to a breast fed infant can be minimized by temporary discontinuation of breastfeeding (*see Clinical Considerations)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tc-99m exametazime, any potential adverse effects on the breastfed child from Tc-99m exametazime or from the underlying maternal condition.

Clinical Considerations

To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breastmilk after the administration of technetium Tc 99m exametazime-labeled leukocytes for 12 to 24 hours, where the duration corresponds to the typical range of administrated activity, 259 MBq to 925 MBq (7mCi to 25mCi).

8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

17 PATIENT COUNSELING INFORMATION

Pregnancy

- Advise pregnant women of the risk of fetal exposure to radiation doses if they undergo a radionuclide procedure *[see Use in Specific Populations (8.1)]*.

Lactation

- Advise lactating women that exposure to Tc99m (b) (4) through breast milk can be minimized if breastfeeding is (b) (4) when Tc99m exametazime (b) (4) administered. Advise a lactating woman to pump and discard breast milk for 12-24 hours (b) (4) *[see Use in Specific Populations (8.2)]*.

APPENDIX A – Applicant's Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
Lactation: Temporarily discontinue breastfeeding. (8.2)

FULL PRESCRIBING INFORMATION

(b) (4)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

(b) (4)

Data

Human Data

Limited published literature describes Tc-99m exametazime crossing the placental barrier and accumulating in the fetal liver. 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.

8.2 Lactation

Risk Summary

(b) (4)

8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established. (b) (4)

17 PATIENT COUNSELING INFORMATION

Pregnancy

- Advise pregnant women of the risk of fetal exposure to radiation doses if they undergo a radionuclide procedure (b) (4) *[see Use in Specific Populations (8.1)]*.

Lactation

- (b) (4)

Appendix B

ICRP (2000, 2008)[6,7]
ICRP Approximate Fetal Doses from Common Diagnostic Procedures

Table 1. Approximate foetal doses from common diagnostic procedures in the United Kingdom. (Adapted from Sharp, Shrimpton, and Buiy, 1998)

Examination	Mean (mGy)	Maximum (mGy)
Conventional x-ray examinations		
Abdomen	1.4	4.2
Chest	< 0.01	< 0.01
Intravenous urogram	1.7	10
Lumbar spine	1.7	10
Pelvis	1.1	4
Skull	< 0.01	< 0.01
Thoracic spine	< 0.01	< 0.01
Fluoroscopic examinations		
Barium meal (UGI)	1.1	5.8
Barium enema	6.8	24
Computed tomography		
Abdomen	8.0	49
Chest	0.06	0.96
Head	< 0.005	< 0.005
Lumbar spine	2.4	8.6
Pelvis	25	79

Table 2. Fetal whole body dose from common nuclear medicine examinations in early pregnancy and at term. (Dose includes maternal and fetal self dose contributions. Adapted from Russell, Stabin, Sparks et al., 1997, ICRP, 1988, and ICRP, 1998.)

Radiopharmaceutical	Procedure	Administered activity (MBq)	Early (mGy)	9 months (mGy)
^{99m}Tc	Bone scan (phosphate)	750	4.6–4.7	1.8
^{99m}Tc	Lung perfusion (MAA)	200	0.4–0.6	0.8
^{99m}Tc	Lung ventilation (aerosol)	40	0.1–0.3	0.1
^{99m}Tc	Thyroid scan (pertechnetate)	400	3.2–4.4	3.7
^{99m}Tc	Red blood cell	930	3.6–6.0	2.5
^{99m}Tc	Liver colloid	300	0.5–0.6	1.1
^{99m}Tc	Renal DTPA	750	5.9–9.0	3.5
^{67}Ga	Abscess/tumour	190	14–18	25
^{123}I	Thyroid uptake[1)]	30	0.4–0.6	0.3
^{131}I	Thyroid uptake[1)]	0.55	0.03–0.04	0.15
^{131}I	Metastases imaging[1)]	40	2.0–2.9	11.0

[1)] Fetal thyroid doses are much higher than fetal whole body dose, viz. 5–15 mGy/MBq for ^{123}I and 0.5–1.1 Gy/MBq for ^{131}I.

Appendix C[20]

USNRC – Activities of Radippharmaceuticals that Require Instructions for Breastfeeding

Table U.3 Activities of Radiopharmaceuticals That Require Instructions and Records When Administered to Patients Who Are Breast-Feeding an Infant or Child

Radionuclide	COLUMN 1 Activity Above Which Instructions Are Required		COLUMN 2 Activity Above Which a Record is Required		COLUMN 3 Examples of Recommended Duration of Interruption of Breast-Feeding
	(MBq)	(mCi)	(MBq)	(mCi)	
I-131 NaI	0.01	0.0004	0.07	0.002	Complete cessation (for this infant or child)
I-123 NaI	20	0.5	100	3	
I-123 OIH	100	4	700	20	
I-123 MIBG	70	2	400	10	24 hours for 370 MBq (10 mCi) 12 hours for 150 MBq (4 mCi)
I-125 OIH	3	0.08	10	0.4	
I-131 OIH	10	0.3	60	1.5	
Tc-99m DTPA	1000	30	6000	150	
Tc-99m MAA	50	1.3	200	6.5	12.6 hours for 150 MBq (4 mCi)
Tc-99m Pertechnetate	100	3	600	15	24 hours for 1,100 MBq (30 mCi) 12 hours for 440 MBq (12 mCi)
Tc-99m DISIDA	1000	30	6000	150	
Tc-99m Glucoheptonate	1000	30	6000	170	
Tc-99m MIBI	1000	30	6000	150	
Tc-99m MDP	1000	30	6000	150	
Tc-99m PYP	900	25	4000	120	
Tc-99m Red Blood Cell *In Vivo* Labeling	400	10	2000	50	6 hours for 740 MBq (20 mCi)
Tc-99m Red Blood Cell *In Vitro* Labeling	1000	30	6000	150	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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Division of Medical Imaging Products (DMIP)
Radiation Dosimetry, Dose, and Safety Report
NDA 208870
FDA/CDER/OND/ODE-IV/DMIP
March 23, 2017

From:	Stanley H. Stern, Ph.D., DMIP Health Physicist
Through:	Alex Gorovets, M.D., Ph.D., DMIP Deputy Director
To:	Michele B. Fedowitz, M.D., DMIP Associate Director for Labeling
Subject:	Sections on *Radiation Dosimetry* and on *Lactation* in the draft prescribing information for ^{99m}Tc exametazime kit for leukocyte radiolabeling
Sponsor:	Jubilant DraxImage Inc.
Input requested:	January 23, 2017
Desired completion:	March 31, 2017

Conclusions and recommendations

Radiation dosimetry and absorbed dose: The table of absorbed dose proposed by the sponsor [1] is based on (b) (4) Estimates based on measurements [6, 7] with subjects who've been administered Tc-exametazime-radiolabeled leukocytes are likely to be more accurate than those of the sponsor proposal. Absorbed-dose estimates based ^{99m}Tc measurements [6, 7] are developed in Table 1 of the following analysis, and we recommend them for the prescribing information.

Interruption of lactation: The modeling and major assumptions of the guidance NUREG-1492 [12] and the data it cites for pertechnetate, presumed to be the radioactive moiety excreted to breast milk from women intravenously administered ^{99m}Tc-labeled leukocytes, remain reasonable in the context of the seemingly limited amount of pertinent data acquired over the past 20 years and still current. Therefore the associated recommendations in the guidance NUREG-1556 [11] for interruption of breast feeding by females receiving ^{99m}Tc-labeled leukocytes – based on the NUREG-1492 [12] data, analysis, and modeling – are reasonably valid as well. We recommend adapting the NUREG-1556 [11] recommendations by modifying the Lactation section of the prescribing information so that it is consistent with the following text:

"To decrease radiation exposure to the breastfed infant, advise a lactating woman to pump and discard breast milk after the administration of technetium Tc 99m exametazime-labeled leukocytes for 12 to 24 hours, where the duration corresponds to the typical range of administered activity, 259 MBq to 925 MBq (7 mCi to 25 mCi)."

Note that for this particular range of recommended activity, the range of interruption represents a safeguard against absorbed dose that could be incurred by a breast-feeding infant that is close to but somewhat more protective than the recommendations in Table U-3 of NUREG-1556 [11], Appendix U for Tc-99m-labeled white blood cells.

Analysis of radiation dosimetry and absorbed dose

139 of the 140 data entries of Table 1, "Absorbed doses: Tc-99m White Blood cells (Leukocytes)," in the sponsor's October 2016 draft of prescribing information [1] (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) one would expect better accuracy were absorbed-dose values determined, for example, following whole-body imaging and blood sampling of humans injected with leukocytes radiolabeled particularly with ^{99m}Tc-*exametazime*.

We found two papers with such organ-dose estimates [6, 7]. In order to develop the following Table 1 of absorbed dose per administered activity of ^{99m}Tc-exametazime-labeled leukocytes, we weighted the estimates in these two papers according to the following considerations:

- While the parent data-populations respectively associated with references [6] and [7] are related, they are not necessarily identical. These populations differ through (1) differing radiolabeling formulations (i.e., non-stabilized versus stabilized ^{99m}Tc-exametazime-labeled leukocytes) and (2) differing methodological approaches in dosimetry (e.g., in the way activity residence times in source organs were evaluated and in the resulting differences between their magnitudes), as well in the numbers of study subjects – **5** subjects in reference [6], **10** subjects in reference [7].
- We estimated an *overall* population mean from a weighted sum for the **15 subjects**, the pooled total number of participants in both studies. For each organ dose (per administered activity), an overall population mean was estimated as the sum of a reference-[6] mean

(b) (4)

value weighted by the fraction 5/15 = 1/3 plus the corresponding reference-[7] mean value weighted by the fraction 10/15 = 2/3.

- For each organ we equated the overall mean value of absorbed dose per unit administered activity with the arithmetic average of two values corresponding to the respective weighted means inferred from references [6] and [7], where (significant) differences between these two weighted means are reflective of the differing formulations and dosimetric methodologies. We assumed that each pair of values of organ-dose (per administered activity) comprises a sample of two data points from which a standard deviation of the overall mean can be estimated. For each organ we furthermore estimated a value of the standard deviation (SD) for a presumed distribution corresponding to the pooled sample of 15-subject data points overall in the two studies: SD is the product of $(15)^{1/2}$ and the estimated standard deviation of the overall mean [8].
- For all organs, the *average value of the ratio* of the standard deviation of the distribution of values of absorbed dose per administered activity to the overall mean is **2.7**. (The estimated standard deviation of the mean for this mean ratio is estimated to be 0.4, and the standard deviation of the distribution of ratio values organ-by-organ is estimated to be 1.6.) Although the average value (2.7) of the ratio is much larger than that value (≈ 0.7) of the ratio which would be inferred from *just one* [7] of the two studies of our analysis, in light of the differing product formulations and methodological approaches to dosimetry between the *two studies*, the value 2.7 and the magnitudes of associated statistics are relatively consistent (b) (4)

Table 1. ^{99m}Tc-exametazime-labeled white blood cells (leukocytes)*

Organ	Overall Mean absorbed dose per unit activity administered, adult (μGy/MBq)	Overall Mean absorbed dose per unit activity administered, adult (mrad/mCi)	(b) (4)
Spleen	88	327	
Red marrow	15	54	
Liver	13	48	
Bone surfaces	8.4	31	
Urinary bladder	8.2	30	
Lungs	7.4	27	
Stomach	6.7	25	
ULI	5.5	20	
Colon***	4.5	17	
LLI	3.3	12	
SI	2.5	9.3	
Ovaries	1.6	6	
Thyroid	1.3	4.8	
Breast	0.9	3.3	
Testes	0.8	3	
Kidneys	0.3	1.1	
Remaining Organs****	2.2	8.1	
Effective dose per administered activity	**7.5 μSv/MBq**	**28 mrem/mCi**	

*Adapted from references [6] and [7] according to the preceding considerations.

(b) (4)

***Estimated from the upper large intestine (ULI) and lower large intestine (LLI) values of absorbed dose (D) according to reference [2], equation 6.3, paragraph 62, p. 31: $D_{colon} = 0.57\ D_{ULI} + 0.43\ D_{LLI}$.

****The reference [7] value for "total body" dose per administered activity is applied here, together with the reference [6] value for "Remaining Organs," to estimate the overall mean and associated ratio of the estimated S.D. to the overall mean for a pooled-data category nominally denoted "Remaining Organs."

Analysis of recommendations regarding interruption of lactation

The U.S. Nuclear Regulatory Commission (NRC) has issued regulations [9, 10] and comprehensive guidance [11] for its medical licensees to manage the discharge of patients (or medical research subjects) who have been administered radioactive substances in the course of clinical diagnosis, treatment, or research. The objective is to protect individual members of the public from irradiation associated with the radioactive substances that patients and research subjects still retain (and ultimately eliminate) starting from the time of their release from the

clinic and thereafter.

Reference [9] includes the general regulations to protect individual members of the public. Reference [10] specifies particular regulations related to release of patients or medical-research participants who contain radioactive substances: While a patient or research subject may be released if the **total effective dose equivalent (TEDE)**[b] to any other individual exposed to the person released is not likely to exceed 5 mSv, there are special requirements if the TEDE is likely to exceed 1 mSv. In that case the licensee needs to provide the released individual (or that person's parent or guardian) with instructions on reducing exposure to other individuals. If a nursing infant or child could incur a TEDE exceeding 1 mSv (under an assumption of no interruption in breast-feeding), then the instructions must also include guidance on interrupting or discontinuing breast-feeding and on potential consequences, if any, of failure to follow the guidance. The licensee is also required to keep records of the basis for authorizing patient release and of the instructions provided to a breast-feeding female.

NRC guidance NUREG-1556 Vol. 9, Rev. 2, contains Appendix U, "Model Procedure for Release of Patients or Human Research Subjects Administered Radioactive Materials" [11]. Table U.3 ("Activities of Radiopharmaceuticals That Require Instructions and Records When Administered to Patients Who Are Breast-Feeding an Infant or Child") includes (page U-10) entries for Tc-99m-radiolabeled white blood cells. Table-U.3 columns 1 and 2 delineate values of administered activity above which patient instructions and a record are respectively required. Column 3 cites examples of the recommended duration of interruption of breast-feeding. For Tc-99m-labeled white blood cells, the particular durations listed are 24 hours for 1100 MBq (30 mCi) administered activity and 12 hours for 440 MBq (12 mCi) administered activity. ***Table-U.3 footnotes advise that the duration of interruption of breast-feeding is selected to reduce the maximum TEDE to a newborn infant to less than 1 mSv, and actual doses would be far below 1 mSv***. Hence, a maximum incurrence of 1 mSv TEDE in a breast-feeding infant has been a *de facto* standard in general for recommendations of how long breast feeding should be interrupted or possibly discontinued following the diagnosis or treatment of lactating females receiving radioactive substances in the course of clinical diagnosis, treatment, or research.

The calculational basis of the NUREG-1556 breast-feeding recommendations are detailed in reference [12], which includes references to measured data for excretion of radiopharmaceuticals in breast milk. Reference-[12] modeling and calculations are applied to radiation absorbed-dose estimates from the review chapter by Stabin [13].

With regard to ^{99m}Tc-labeled leukocytes, references [11] and [12] include two major assumptions in the calculations which comprise the basis of the recommendations for interrupting breast feeding:

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[b] Per https://www.nrc.gov/reading-rm/basic-ref/glossary/total-effective-dose-equivalent-tede.html, the Total Effective Dose Equivalent (TEDE) is the sum of the effective dose equivalent (for external exposures) plus the committed effective dose equivalent (for internal exposures). TEDE is related to what the International Commission on Radiological Protection (ICRP Publication 103, 2007) defines as "radiation detriment," a quantitative index of the potentially harmful effects of radiation, associated with the "incidence of radiation-related cancer or heritable effects, lethality of these conditions, quality of life, and years of life lost owing to these conditions."

1) It is assumed that the activity released in breast milk is solely in the form of pertechnetate ($^{99m}TcO_4^-$) [11, 12].

2) Furthermore, for *all* of the radiopharmaceutical products covered at the time (early 1995) of the NUREG-1492 [12] literature search, which turned up "no information in the literature describing uptake of ingested radiopharmaceuticals from the infant gastrointestinal tract" [12], it was assumed that "100 percent of the ingested activity" is "quickly and completely absorbed from the infant's GI tract" [12]. Hence the radiation dose estimates [13, Table 26.19, and reference 45 cited therein] applied to model oral ingestion of breast milk by newborns and one-year-olds are actually, as a necessity for lack of more pertinent data, based [12] on ^{99m}Tc as sodium pertechnetate administered *intravenously* in those infants.

Since the mid-1990s there has been a significant advance in understanding that breast milk contains immunologic factors – including leukocytes – among many other "bioactive components that safeguard infant growth and development" [14]. In other words, it is possible that ^{99m}Tc exametazime-labeled leukocytes are ingested by an infant following a nuclear medicine exam of a lactating female, since in "early lactation, the breastfed infant may consume as many as 10^{10} maternal leukocytes per day" [14]. But the identity of the form of the ^{99m}Tc in breast milk following intravenous administration of ^{99m}Tc exametazime-labeled leukocytes in the lactating female is ambiguous: For the only patient in a recent study [15] who received intravenous administration of ^{99m}Tc-HMPAO-labeled leukocytes,

> "…the fraction of the administered activity excreted in the breast milk was 0.11%. The effective half-time of the activity concentration was virtually the same as the physical half-life; no biological excretion or redistribution was seen in the patient. It is not clear whether the activity ingested by the infant was in the form of ^{99m}Tc-pertechnetate, ^{99m}Tc-HMPAO, or ^{99m}Tc-HMPAO-leucocytes. Marshall et al…." [16] "…reported a total excretion fraction…" equal to 0.15% "…after intravenous injection of ^{99m}Tc-HMPAO in a brain perfusion study. Assuming that the activity in the breast milk was in the form of ^{99m}Tc-pertechnetate, the effective dose to the infant was 2.0×10^{-4} $mSv_{infant}/MBq_{mother}$."

We summarize these findings [15, 16] with respect to the modeling and calculations of NUREG-1492 [12] and related sources along the following analytical lines:

- To within the multiple factors and large variations confounding such comparisons, the fraction (0.11%) of administered activity excreted into breast milk of the patient who received ^{99m}Tc-exametazime-labeled leukocytes [15], as well as the fraction (0.15%) excreted from the patient who received ^{99m}Tc-HMPAO in a brain-perfusion study [16], are consistent in magnitude with the lower bound of the range (0.16% – 6.76%) reported in NUREG-1492 [12] from the compilation of eight pertechnetate studies (1973-1987) of activity excretion into breast milk.

- However, the magnitude 0.11% (or 0.15%) seems significantly smaller than the fractions measured [15] for the ranges of activity excreted into breast milk from pertechnetate administered, respectively, following pretreatment with a thyroid blocking agent (0.68% – 0.95%) versus with no blocking agent (5.3% – 19%).

- A simple comparison of estimates of various magnitudes of effective dose (E) or of effective dose equivalent (EDE) in neonates and one-year-olds per activity of pertechnetate [2, 13, 15], ^{99m}Tc-exametazime (HMPAO) [2, 13], ^{99m}Tc-exametazime-

labeled leukocytes [15], or ^{99m}Tc-labeled leukocytes [2, 13] *intravenously injected in those infants* – the values of which estimates are applied in the modeling of absorbed dose associated with oral ingestion of breast milk – indicates a range of variation much smaller than the variation of activity excretion into breast milk: For neonates, the values of E/activity and EDE/activity range from 0.11 to 0.31 $mSv_{infant}/MBq_{infant}$ (a factor of 2.8), and for one-year-olds, they range from 0.049 to 0.12 $mSv_{infant}/MBq_{infant}$ (a factor of 2.4). In comparison [15], "The initial activity concentration in the breast milk varied considerably from approximately 10^{-7} to 10^{-3} MBq/MBq administered to the mother per millilitre of milk, i.e. four orders of magnitude, after administration of the different ^{99m}Tc-labelled compounds. Also, individual variation by a factor of up to 10 between mothers given the same radiopharmaceutical was observed. The effective half-time, however, did not vary so widely (2.7 – 7.5 h). An effective half-time exceeding the physical half-life of ^{99m}Tc was obtained for one of the radiopharmaceuticals and was most likely a result of delayed breakdown of the compound leading to increased release of free pertechnetate with time."

- The preceding points suggest that estimation of the range of effective dose (or effective dose equivalent) in infants per activity injected into lactating females is uncertain primarily in association with the large variations in activity excretion into breast milk and in the ambiguous identity of the radioactive moiety. For ^{99m}Tc exametazime-labeled leukocytes, when observations of breast-milk fraction of activity are applied to dose estimates, the recent study [15] reports a value of 0.20 $\mu Sv_{infant}/MBq_{mother}$, while for unblocked pertechnetate the range is (9.9 – 36) $\mu Sv_{infant}/MBq_{mother}$. NUREG-1492 [12] reports a range (for pertechnetate excreted into breast milk from ^{99m}Tc-labeled leukocytes) of (0.18 – 7.42) $\mu Sv_{infant}/MBq_{mother}$ for a neonate and (0.083 – 3.44) $\mu Sv_{infant}/MBq_{mother}$ for a one-year-old.

Hence, our analysis suggests that

1) The NUREG-1492 [12] modeling and its major assumptions – namely, excretion of pertechnetate into breast milk with the activity quickly and completely absorbed from the GI tract – remain reasonable in the context of the seemingly limited amount of pertinent data acquired over the past 20 years and still current. There is much uncertainty associated with the magnitudes of activity excreted into breast milk, the chemical forms of the excreted radioisotopes, their biokinetic distributions from oral ingestion, and their uptakes and elimination by nursing infants.

2) Therefore, the NUREG-1492 [12] ranges of activity and effective doses in nursing infants for ingestion of breast milk containing $^{99m}TcO_4$ from ^{99m}Tc-exametazime-labeled leukocytes intravenously administered to lactating females overlap to an extent with current estimates [15] and are reasonably valid; and

3) The associated recommendations in NUREG-1556 [11] for interruption of breast feeding by females receiving ^{99m}Tc-labeled leukocytes, based on the data, analysis, and modeling described in NUREG-1492 [12], are reasonably valid as well.

References

[1] NDA 208870, Draft prescribing information for the DraxImage Inc. kit for the preparation of technetium (Tc 99m) exametazime for leukocyte labeling, October 5, 2016, October 5, 2016.

[2] ICRP Publication 128, *Radiation Dose from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances*, Approved by the International Commission on Radiological Protection in July 2014, *Annals of the ICRP*, Vol. 44, No. 2S, Sage Journals, 2015.

[3] ICRP Publication 53, *Radiation Dose to Patients from Radiopharmaceuticals*, *Annals of the ICRP*, Vol. 18, Issues 1-4, published for the International Commission on Radiological Protection by Pergamon Press, 1987/8.

[4] C. Morillon, M.M. Bé, V. Chechev, A. Egorov, "^{99m}Tc – Comments on evaluation of decay data," Dec 2000, with half-life update Jan 2004, http://www.nucleide.org/DDEP_WG/Nuclides/Tc-99m_com.pdf, from *Recommended Data* of the *Table de Radionucléides*, Laboratoire National Henri Becquerel, Commissariat à l'Énergie Atomique (CEA), Saclay, France, http://www.nucleide.org/DDEP_WG/DDEPdata.htm, Oct 4, 2016.

[5] V.P. Chechev, http://www.nucleide.org/DDEP_WG/Nuclides/In-111_tables.pdf, Sep 29, 1998- April 26, 2006, from *Recommended Data* of the *Table de Radionucléides*, Laboratoire National Henri Becquerel, Commissariat à l'Énergie Atomique (CEA), Saclay, France, http://www.nucleide.org/DDEP_WG/DDEPdata.htm, Mar 3, 2017.

[6] M.L. Brown, J.C. Hung, R.J. Vetter, M.K. O'Connor, S. Chowdhury, and L.A. Forstrom, "The Radiation Dosimetry and Normal Value Study of ^{99m}Tc-HMPAO-Labeled Leukocytes," *Investigative Radiology*, Vol. 29, No. 4, pp. 443-447, April 1994.

[7] Peter D. Robins, Isabel Salazar, Lee A. Forstrom, Brian P. Mullan, and Joseph C. Hung, "Biodistribution and Radiation Dosimetry of Stabilized ^{99m}Tc-Exametazime-Labeled Leukocytes in Normal Subjects," *The Journal of Nuclear Medicine*, Vol. 41, No. 5, pp. 934-940, May 2000.

[8] Philip R. Bevington and D. Keith Robinson, *Data Reduction and Error Analysis for the Physical Sciences*, Third Edition, Chapter 4, "Estimates of Mean and Errors," pp. 51-74, McGraw-Hill, 2003.

[9] 10 CFR 20 Subpart D—*Radiation Dose Limits for Individual Members of the Public*.

[10] 10 CFR 35.75 *Release of individuals containing unsealed byproduct material or implants containing byproduct material*.

[11] D.B. Howe, M. Beardsley, and S. Bakhsh, *Consolidated Guidance About Materials Licenses. Program-Specific Guidance About Medical Use Licenses. Final Report*, NUREG-1556, Vol. 9, Rev. 2, including Appendix U – "Model Procedure for Release of Patients or Human Research Subjects Administered Radioactive Materials," U.S. Nuclear Regulatory Commission, January 2008; https://www.nrc.gov/reading-rm/doc-collections/nuregs/staff/sr1556/v9/, web page last reviewed/updated August 1, 2016.

[12] S. Schneider and S.A. McGuire, *Regulatory Analysis on Criteria for the Release of Patients Administered Radioactive Material*, NUREG-1492, Final Report, U.S. Nuclear Regulatory Commission, February 1997.

[13] Michael G. Stabin, Chapter 26, pp. 556-581, "Internal Dosimetry in Pediatric Nuclear Medicine," in *Pediatric Nuclear Medicine*, edited by S.T. Treves, M.D., Springer-Verlag, New York, 1995.

[14] Olivia Ballard and Ardythe L. Morrow, "Human Milk Composition. Nutrients and Bioactive Factors," *Pediatric Clinics of North America*, Vol. 60, Issue 1, pp. 49-74, February 2013.

[15] Sigrid Leide-Svegborn, Lars Ahlgren, Lennart Johansson, and Sören Mattsson, "Excretion of radionuclides in human breast milk after nuclear medicine examinations. Biokinetic and dosimetric data and recommendations on breastfeeding interruption," *European Journal of Nuclear Medicine and Molecular Imaging*, Vol. 43, Issue 5, pp. 808-821, May 2016.

[16] D.S.C. Marshall, N.R. Newberry, and P.J. Ryan, "Measurement of the secretion of technetium-99m hexamethylpropylene amine oxine into breast milk," *European Journal of Nuclear Medicine*, Vol. 23, No. 12, pp. 1634-1635, Dec 1996.

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03/23/2017

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03/24/2017

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03/24/2017

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: March 22, 2017

To: Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products (DMIP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Kit for the Preparation of Technetium (Tc99m) Exametazime for Leukocyte Labeling, for intravenous injection
NDA 208870
OPDP Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on July 22, 2016, for the Kit for the Preparation of Technetium (Tc99m) Exametazime for Leukocyte Labeling, for intravenous injection. Our comments, provided directly on the attached marked-up copy of the proposed PI, are based on the proposed labeling emailed to us on March 14, 2017.

Carton and Container Labeling

OPDP notes that the proposed carton and container labeling, submitted by the sponsor on September 15, 2016, includes a part of the indication for the drug. Specifically, the "Carton Box Labeling" includes the following claim, "(b) (4) ", but omits important material facts with respect to consequences that may result from the use of the drug as recommended or suggested on the package labeling. Therefore, please consider either deleting the claim or revising the proposed "Carton Box Labeling" by including the full indication along with sufficient disclosure of the most serious and most common risks associated with the drug in depth and in detail to balance the above claim.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
03/22/2017

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:	November 22, 2016
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 208870
Product Name and Strength:	Kit for the Preparation of Technetium Tc99m Exametazime (b) (4)
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Jubilant Draximage, Inc.
Submission Date:	July 20, September 15, and October 5, 2016
OSE RCM #:	2016-1660
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 REASON FOR REVIEW

The Division of Medical Imaging Products (DMIP) has requested DMEPA to review the label and labeling for NDA 208870 Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) submitted by Jubilant Draximage, Inc. We have reviewed the proposed carton and container labeling and kit labels/worksheets as well as 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
Human Factors Study	C-N/A
ISMP Newsletters	D
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 for label and labeling reviews unless we are aware of medication errors through our routine post market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), carton label, container label and kit labels/worksheets for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) The risk assessment was completed to identify deficiencies that may lead to medication errors. DMEPA identified areas of improvement in the labels and labeling that can be improved to increase the readability and prominence of important information.

We provide recommendations in Section 4.1 for the Prescribing Information and Section 4.2 for the container label, carton labeling and Leukocyte Labeling Schematic to improve the readability and prominence of important product information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendation in Section 4.1 for the PI and 4.2 for the container label and carton labeling to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. PRESCRIBING INFORMATION (PI)

I. HIGHLIGHTS: DOSAGE FORMS AND STRENGTHS

1. Dangerous abbreviations, symbols, and dose designations that are included in Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols and Dose Designations[a] appear in the Dosage and Administration section of Highlights. As part of a national campaign to avoid the use of dangerous dose designations, FDA agreed not to approve such error dose designations in the approved labeling of products. Thus, remove all instances of trailing zeros (e.g. 2.00 GBq).

III. SECTION 16 HOW SUPPLIED/STORAGE AND HANDLING

1. Kit components in section 16.1, How Supplied, should include appropriate package type terms, complete product strengths and NDC. Revise to include: :
    - The DRAXIMAGE Exametazime kit comprises (NDC___-__-__):
    - 5 Single-Dose 0.5 mg/vial sterile, non-pyrogenic and lyophilized mixture of exametazime, 7.(b)(4)mcg stannous chloride dehydrate and 4.5 mg sodium chloride (NDC for vial___-__-__).

4.2 RECOMMENDATIONS FOR JUBILANT DRAXIMAGE, INC

We recommend the following be implemented prior to approval of this NDA 208870:

A. CARTON LABELS

1. Bold and increase the font size of the strength 0.5 mg/vial on the principal display panel (PDP) to highlight the prominence of this important information.

2. To avoid a ten-fold misinterpretation of strength or dose, as referenced in ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designations, remove trailing zeros (e.g. 4.0 mcg per vial) from carton labeling.

3. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear on the carton labeling. As part of a

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 April 2]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows: Replace all "µg" symbols appearing on the carton with "mcg".

4. Revise the statement (b) (4) to use positive language. E.g., (b) (4) We recommend this revision due to post-marketing reports that negative statements may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpret the warning as an affirmative action.

5. Although 21CFR 201.25 does not apply to radiopharmaceuticals, barcode technology has been shown to be an important component of drug safety. Once a radiopharmaceutical product is placed into the lead shield, the label cannot be properly visualized for verification. In the absence of a barcode, accurate vial selection is reliant on error prone procedural and visual verification alone. We recommend the addition of a barcode to the carton labeling. (See Appendix D).

B. CONTAINER LABELS

1. The container label of one unit and the carton labeling of 5 units should have different NDC numbers. Revise the NDC numbers so that the carton labeling and container label NDC numbers are different for these two package configurations.

2. See A.5.

C. LEUKOCYTE LABELING SCHEMATIC

1. Part 1, Step 2 the syringe is pointing to (b) (4) Please correct the image to either remove the human outline or have the syringe pointing to the inner elbow.

2. The step for replacing needle with winged infusion set is missing. Add a step between Step 5 and 6 to illustrate the replacement of the needle with the winged infusion set.

3. Key information for placing the syringe in a lead shielded container is missing in Part 2, Step 20. We recommend adding the statement: "Place syringe in a

lead shielded container to align with both steps of the LD's schematic and the image instructions."

4. Part 2, Step 21 the syringe is pointing to the upper bicep for administration, implying intramuscular injection. Correct the image to align with intravenous administration by having the syringe point to the inner elbow.

5. APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Draximage Exametazime (Kit for the Preparation of Technetium (Tc 99m) Exametazime (b) (4) that Jubilant DraxImage Inc. submitted on July 20, 2016 and the listed drug (LD).

Table 2. Relevant Product Information for Draximage Exametazime (Kit for the Preparation of Technetium (Tc 99m) Exametazime (b) (4) **and the Listed Drug**

Product Name	Draximage Exametazime (Kit for the Preparation of Technetium (Tc 99m) Exametazime (b) (4)	Ceretec (Kit for the Preparation of Technetium (Tc 99m) Exametazime Injection)
Initial Approval Date	N/A	December 30, 1988
Active Ingredient	Exametazime	
Indication	1. Leukocyte labeled scintigraphy as an adjunct in the localization of infection, (b) (4) intra-abdominal infection, inflammatory bowel disease (b) (4)	1. Adjunct in the detection of altered regional cerebral perfusion in stroke. 2. For leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.
Route of Administration	IV	
Dosage Form	Single use vial of sterile, non-pyrogenic and lyophilized mixture of exametazime, stannous chloride dehydrate and sodium chloride for reconstitution	Single use vial of sterile, non-pyrogenic and freeze dried mixture of exametazime, stannous chloride dehydrate and sodium chloride powder for reconstitution
Strength	0.5 mg/ vial (0.37 GBq up to 2 GBq (10mCi up to 54 mCi))	
Dose and Frequency	normal adult (70 kg) dose is 0.259-0.925 GBq (7-25 mCi)	For leukocyte labeled scintigraphy: normal adult (70 kg) dose is 0.259-0.925 GBq (7-25 mCi) For detection of altered regional cerebral perfusion: average adult (70 kg) is 370-740 MBq (10-20 mCi)

How Supplied	Kit Contains: 1. 5-single use vials 2. (b) (4) radiation labels 3. 5 labeling efficiency /Radiochemical purity worksheets 4. 1 Leukocyte Labeling Schematic 1 Package insert
Storage	Store kit at 15°-25°C (59°-77°F). Store the formulated drug for up to 30 minutes at 20°-25°C (68°-77°F) using appropriate radiation shielding.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 18, 2016, we searched the L:drive and AIMS using the terms*, Exametazime*, *Draximage Exametazime*, *Kit for the Preparation of Technetium Tc 99m Exametazime* (b) (4) *and Ceretec* to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On August 22, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Pennsylvania Patient Safety Advisory, Acute Care Newsletter, Long-term Care Newsletter, Canada Safety Bulletin, Community Newsletter, Nursing Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Exametazime, Kit for the preparation of Technetium (Tc 99m) Exametazime (b) (4) Technetium, Ceretec

D.2 Results

Our search resulted in one relevant safety-brief article in the October 6, 2011 (Volume 16, Issue 15) ISMP Medication Safety Alert. The safety-brief outlines an error that occurred in a nuclear pharmacy when one formulation of a Technetium Tc 99m product was inadvertently selected instead of the correct one.

A vial of DraxImage DTPA (Technetium TC 99m pentetate injection) was placed in a leaded vial shield instead of DraxImage MDP-25 (Technetium TC 99m medronate injection). Both vials have green caps and green and white labels, it was reported that the pharmacist did not notice the error during visual verification before placing the DTPA into the shield. Both products perform the same in radiochemical purity testing; therefore the error was not discovered during this procedural step. The error was discovered when nuclear medicine customers reported altered bio- distribution to the pharmacy once the product was administered to the patient. The error resulted in 12 incidences of non-diagnostic images and all patients had to undergo rescan.

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,[b] along with postmarket medication error data, we reviewed the following Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) labels and labeling submitted by Jubilant Draximage Inc. on July 20, 2016.

- Prescribing Information
- Container label
- Carton labeling
- Leukocyte Labeling Schematic
- Radiation Label
- Radiochemical Purity Worksheet
- Labeling Efficiency Worksheet

G.2 Label and Labeling Images

Prescribing Information

Container Labeling

(b) (4)

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

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/s/

IDALIA E RYCHLIK
11/22/2016

HINA S MEHTA
11/22/2016

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208870

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Kit for the Preparation of Technetium Tc99m Exametazime

Applicant: Jubilant DraxImage

Receipt Date: July 20, 2016

Goal Date: May 19, 2017

1. Regulatory History and Applicant's Main Proposals

On July 20, 2016 Jubilant DraxImage submitted a 505(b)(2) application to the Division of Medical Imaging Products. The proposed indication is for WBCs [leukocytes] labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease. The relied upon product for this application is NDA 19829 Ceretec.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 7, 2016. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: (b) (4)

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment: *Some cross references in the FPI are the subsections and not the sections*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

NO 37. If no Contraindications are known, this section must state "None."

Comment: *Cross reference needs to be removed*

ADVERSE REACTIONS Section in the FPI

N/A 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERTA E DAVIS WARREN
09/15/2016

KYONG A KANG
09/15/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208870 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: N/A Established/Proper Name: Kit for the Preparation of Tc99m Exametazime (b) (4) Dosage Form: Lyophilized (b) (4) Strengths: N/A. Each vial contains 0.5 mg/vial		
Applicant: Jubilant DraxImage Agent for Applicant (if applicable): INC Research LLC		
Date of Application: 7-15-16 Date of Receipt: 7-20-16 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: May 20, 2017	Action Goal Date (if different): May 19, 2017	
Filing Date: September 18, 2016	Date of Filing Meeting: August 31, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Indicated WBCs [leukocytes] labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): PIND 123604	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Standard
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		Seeking one of the two approved indications
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		Seeking one of the two approved indications
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		Seeking one of the two approved indications
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested:	☐	☒	☐	

Note: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☐ legible ☒ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications

Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.*
Forms *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	As requested, Sponsor submitted form on 7-22-16
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☒		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	7-29-16 Applicant resubmitted form with signatures from the foreign applicant and US agent.
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Electronic submission
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☐	☒		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMatern

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

alHealthStaff/ucm027829.htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

If no, request applicant to submit SPL before the filing date.				
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☒	☐	☐	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒	☐	☐	Sponsor submitted information 8-30-16
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 14, 2014	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 31, 2016

BACKGROUND: On July 20, 2016 Jubilant DraxImage submitted a 505(b)(2) application to the Division of Medical Imaging Products. The proposed indication is for WBCs [leukocytes] labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease. The relied upon product for this application is NDA 19829 Ceretec. The applicant is seeking one of the two approved indications.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alberta Davis-Warren	Y
	CPMS/TL:	Kyong Kaye Kang, PharmD	Y
Cross-Discipline Team Leader (CDTL)	Danae Christodoulou, PhD		Y
Division Director/Deputy	Libero Marzella, MD, PhD Alex Gorovets, MD		Y N
Office Director/Deputy	Charles Ganley, MD Lesley Furlong, MD		Y N
Clinical	Reviewer:	Phillip Davis, MD	Y
	TL:	Nushin Todd, MD, PhD	Y
Social Scientist Review (*for OTC products*)	Reviewer:		N/A
	TL:		N/A
OTC Labeling Review (*for OTC products*)	Reviewer:		N/A
	TL:		N/A
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		N/A
	TL:		N/A
Clinical Pharmacology	Reviewer:	Sam Habet, PhD	Y
	TL:	Gene Williams, PhD	Y

• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Satish Misra, PhD	Y
	TL:	Jyoti Zalkikar, PhD	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Olayinka Dina, PhD	Y
	TL:	Adebayo Laniyounu, PhD	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Danae Christodoulou, PhD	Y
	RBPM:	Thao Vu, RPh	Y
• Drug Substance	Reviewer:	Martin Haber, PhD	Y
• Drug Product	Reviewer:	Dhana Kasi, PhD	Y
• Process	Reviewer:	Dhana Kasi, PhD	Y
• Microbiology	Reviewer:	Samata Tiwari, PhD	Y
• Facility	Reviewer:	Vidya Pai	N
• Biopharmaceutics	Reviewer:	Poonam Delvadia, PhD	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Adam George	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Idalia Rychlik, PharmD	Y
	TL:	Hina Mehta, PharmD	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Pediatrics *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Ethan Hausman, MD	Y
	TL:	Hari Sachs, MD	N
• Maternal Health *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Jane Liedtka, MD	Y
	TL:	Miriam Dinatale, MD	N
Other attendees	Jagjit Grewal, MPH (ODEIV)		Y
	Eric Duffy, PhD (OPQ)		Y
	Eldon Leutzinger, PhD (OPQ)		Y
	Michele Fedowitz, MD (DMIP)		Y
	Sandra Suarez, PhD (OPQ)		Y
	Meena Ramachandra, PharmD (OPDP)		Y
	Lori Gorski (DPMH)		Y
	Tri Nguyen Bui, PhD, MS (OSE)		
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☒ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information	Reliance on NDA 19829 Ceretec and published literature

described in published literature):	
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No clinical data provided, relied upon NDA 19829 Ceretec	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: this drug/biologic is not first in its class ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The drug is not first in its class
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Libero Marzella, MD, PhD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERTA E DAVIS WARREN
09/15/2016

KYONG A KANG
09/15/2016