CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210828Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: May 2, 2019

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

Diane Hanner, Regulatory Project Manager, DMIP

Michele Fedowitz, Associate Director for Labeling, DMIP

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ga 68 DOTATOC Injection, for intravenous use

NDA: 210828

In response to DMIP's consult request dated July 12, 2018, OPDP has reviewed the proposed product labeling (PI) container labeling for the original NDA submission for Ga 68 DOTATOC Injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMIP on April 24, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed container labeling submitted by the Sponsor to the electronic document room on February 15, 2019, and we do not have any comments.

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

11 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
05/02/2019 02:57:32 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	February 20, 2019
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 210828
Product Name and Strength:	DOTATOC Ga 68 injection 18.5 - 148 MBq/mL (0.5 - 4 mCi/mL) at end of synthesis
Applicant/Sponsor Name:	University of Iowa
FDA Received Date:	February 15, 2019
OSE RCM #:	2018-1109-02
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMORANDUM

Division of Medical Imaging Products (DMIP) requested that we review the revised container label for DOTATOC Ga 68 injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] [b]

2 CONCLUSION

The revised container label for DOTATOC Ga 68 injection is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rychlik, I Label and Labeling Review for Ga-68-DOTATOC injection (NDA 210828). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 17. RCM No.: 2018-1109.
[b] Rychlik, I Label and Labeling Review for Ga-68-DOTATOC injection (NDA 210828). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 12. RCM No.: 2018-1109-01.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 15, 2019

Container labels

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/s/

IDALIA E RYCHLIK
02/20/2019 03:41:41 PM

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02/20/2019 03:49:47 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	February 12, 2019
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 210828
Product Name and Strength:	DOTATOC Ga 68 injection 18.5 - 148 MBq/mL (0.5 - 4 mCi/mL) at end of synthesis
Applicant/Sponsor Name:	University of Iowa
FDA Received Date:	February 6, 2019
OSE RCM #:	2018-1109-01
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMORANDUM

Division of Medical Imaging Products (DMIP) requested that we review the revised container label for DOTATOC Ga 68 injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label is unacceptable from a medication error perspective. Specifically, we note the use of abbreviations which may lead to reader confusion and product administration errors.

3 RECOMMENDATIONS FOR UNIVERSITY OF IOWA

We recommend the following be implemented prior to approval of this NDA 210828:

[a] Rychlik, I Label and Labeling Review for Ga-68-DOTATOC injection (NDA 210828). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 17. RCM No.: 2018-1109.

1. To increase reader comprehension and readability replace the abbreviation 'EOS' with its intended meaning to prevent misinterpretation and confusion. For example, revise "EOS time" and "…mCi/mL @ EOS time" to state "**End of Synthesis Time**" and "**mCi/mL at End of Synthesis Time**", respectively.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBURARY 6, 2019

Container labels

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IDALIA E RYCHLIK
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02/12/2019 06:01:46 PM

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:	October 17, 2018
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 210828
Product Name and Strength:	Ga-68-DOTATOC injection
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	University of Iowa
FDA Received Date:	May 23, 2018
OSE RCM #:	2018-1109
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 REASON FOR REVIEW

On May 23, 2018, the University of Iowa submitted a 505(b)(2) new drug application (NDA 210828) for Ga-68-DOTATOC. Ga-68-DOTATOC injection has been designated as an orphan drug product and is being submitted for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) (b) (4) in adult and pediatric (b) (4) patients.

The Division of Medical Imaging Products (DMIP) requested DMEPA evaluate the proposed Prescribing Information (PI) and Container labeling 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-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our 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) and container label for NDA 210828 to determine if they are acceptable from a medication error perspective. A risk assessment was completed to identify deficiencies that may lead to medication errors.

We identified areas in the PI and container labels that can be improved to increase readability and prominence of important information and further mitigate the risk of medication error. Specifically, we note the PI and the container label contain the use of error prone symbols and abbreviations, as well as, duplicative and text heavy language. These factors may take the readers' attention away from important information such as accurate dosage and administration information, established names, product strength, and expiration information which can lead to reader confusion and inadvertent medication errors.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, carton and container labels are unacceptable from a medication error perspective and can be improved to promote the safe use of the product. We provide recommendations for the PI to the Division in Section 4.1 and for the container label to the University of Iowa in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. General Comments
      a. We recommend the unit of measure be included after each value (e.g. 0.5 mCi/mL to 4 mCi/mL and 18 mSv, 16 mSv and 12 mSv) throughout the PI to prevent confusion.
      b. Consider replacing the symbols '-' with its intended meaning to prevent misinterpretation and confusion.
      c. Drug administration terminology should be accurately defined and aligned throughout the PI (i.e. the use of (b) (4) vs. bolus administration).
   2. Highlights: Dosage and Administration Section
      a. Due to the unique preparation, administration and dosing of the product, limit section to dosing information and direct the healthcare provider to the full prescribing information under Section 2 for complete dosage and administration details.
         i. Limit highlights information to recommended dose information, replace bullet points as follows:
            - Recommended dose in adults is 148 MBq (4 mCi), as a bolus intravenous injection (2.2)
            - Recommended dose in pediatrics is 1.51 MBq (0.043 mCi/kg) with a (b) (4) of 11.1 MBq (0.3 mCi) (b) (4) to 111 MBq (3 mCi), as a bolus intravenous injection (2.2)
            - Initiate imaging 55-90 minutes after administration (b) (4) (2.5)
            - See full prescribing information for preparation and administration information (2)

   3. Highlights: Dosage Forms and Strengths
      a. Revise format to highlight the dosage form and strength as follows:
         Injection: 18.5 MBq/mL to 148 MBq/mL (0.5 mCi/mL to 4 mCi/mL) Ga-68-DOTATOC in multiple dose vials.
   4. Section 2 Dosage and Administration
      a. To ensure important product dosage and administration information is readable and most prominent, relocate (b) (4) and saline flush information (b) (4).

Moreover, delete repetitive information already stated in Section (b) (4) from Section 2.2. Revise section as below:

2.2 Recommended Dosage and Administration Instructions

- (b) (4)
- *After injection of Ga-68-DOTATOC injection, administer an intravenous flush of* (b) (4) *to ensure full delivery of the dose.*
- *Calculate the necessary volume to administer based on measured activity* (b) (4) *, volume, calibration time and date.*

In adults, the recommended amount of radioactivity to be administered for PET imaging is 4 mCi (148 MBq) with a range of 3 mCi to 5 mCi (111 MBq to 185 MBq) administered as an intravenous injection.

In pediatric patients, the recommended amount of radioactivity to be administered for PET imaging is (b) (4) *mCi/kg of body weight (1.59 MBq/kg) with a* (b) (4) *of 0.3 mCi (11.1 MBq)* (b) (4) *to 3 mCi (111 MBq)*

4.2 RECOMMENDATIONS FOR UNIVERSITY OF IOWA HEALTHCARE

We recommend the following be implemented prior to approval of this NDA 210828:

A. Container Labels
    1. To ensure important product information (i.e. product name, product strength, expiration) is readable and most prominent on the container label remove duplicative and unnecessary information from the primary display panel (PDP) as this takes readers' attention away from the important information, such as product names, strengths and expiration:
        a. Delete product (b) (4) information as this should be stated in the prescribing information.
        b. Delete product (b) (4) information, "(b) (4) " and replace with the statement, *See full prescribing information for dosage and administration information.*
    2. Consider Deleting (b) (4) from the upper left hand corner of the label. The information is duplicative and competes for prominence with the product name.
    3. As currently presented the National Drug Code (NDC) is near the product strength information, this may lead to misinterpretation. Relocate the NDC number to top right of the container label, ensure there are no other numbers near the NDC.
    4. Replace the abbreviation 'EOS' with its intended meaning to prevent misinterpretation and confusion.
    5. Highlight the approved route of administration statement by utilizing red font color and placing the "For Intravenous Use Only" statement in a box for prominence.

6. Consider removing [redacted] (b) (4) as it takes readers' attention away from more important information on the label.
7. Decrease the prominence of the manufacturer information (i.e., un-bold and decrease in size) as it takes readers' attention away from more important information on the label.
8. Reformat the expiration statement to allow space for healthcare providers to write date and time on the label. We recommend to revise the expiration statement to read, "Discard after __/__/__ at ___: ___" this presentation will alert the healthcare provider to write a complete date and time on the container label.
9. Align storage information with the prescribing information, include complete temperature range and revise statement to read, "Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F-86°F); Store upright in a lead shielded container."
10. To increase the prominence and readability of the in-use expiration, bold and/or highlight the statement, "Expires 3 hours from end of synthesis" and relocate to the bottom half of the label, following the storage information statement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ga-68-DOTATOC injection received on May 23, 2018 from the University of Iowa.

Table 2. Relevant Product Information for Ga-68-DOTATOC injection	
Initial Approval Date	N/A
Active Ingredient	Ga-68-DOTATOC
Indication	for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) and (b) (4) in adult and pediatric (b) (4) patients.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	18.5 - 148 MBq/mL (0.5 - 4 mCi/mL) at end of synthesis
Dose and Frequency	Adults: 148 MBq (4 mCi) Pediatric: 1.591 MBq/kg (0.043 mCi/kg) with a (b) (4) of 11.1 MBq (0.3 mCi) (b) (4) to 111 MBq (3 mCi)
How Supplied	Multiple-dose glass vial
Storage	in a lead shielded container at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 23, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Gallium, 210828 and Ga 68 DOTCATOC.

Our search identified 0 previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with post-market medication error data, we reviewed the following Ga-68-DOTATOC injection labels and labeling submitted by University of Iowa Healthcare.

- Container label received on May 23, 2018
- Carton labeling received on May 23, 2018
- Prescribing Information (Image not shown) received on May 23, 2018

G.2 Label and Labeling Images

Prescribing Information (Image not shown)

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Container label

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

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/s/

IDALIA E RYCHLIK
10/17/2018

HINA S MEHTA
10/18/2018