CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210828Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	210828
PDUFA Goal Date	May 23, 2019
OSE RCM #	2018-1214 and 2018-1215
Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 19, 2019
Subject	Evaluation of Need for a REMS
Established Name	Ga 68 DOTATOC
Trade Name	
Name of Applicant	University of Iowa Health Care PET Imaging Center
Therapeutic Class	Diagnostic radiopharmaceutical
Formulation(s)	18.5 to 148 MBq/mL (0.5 to 4 mCi/mL) vial
Dosing Regimen	Adults: 148 MBq (4 mCi) intravenous injection Pediatrics: 1.59 MBq/kg (0.043 mCi/kg) with a range of 11.1 MBq (0.3 mCi) up to 111 MBq (3 mCi) intravenous injection

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ga 68 DOTATOC is necessary to ensure the benefits outweigh its risks. University of Iowa Health Care PET Imaging Center submitted a New Drug Application (NDA) 210828 for Ga 68 DOTATOC with the proposed indication for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients (b) (4). The risks associated with Ga 68 DOTATOC include radiation risk and risk of image misinterpretation. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and DMIP agree that a REMS is not necessary to ensure the benefits of Ga 68 DOTATOC outweigh its risks. No serious adverse events were reported in the RET-NET-01 study. The serious risk associated with Ga 68 DOTATOC will be addressed in the warnings and precautions section of the label. The approved radiopharmaceutical agents indium In 111 pentetreotide and gallium Ga 68 dotatate also do not have a boxed warning in their respective labels or have required a REMS for approval.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Ga 68 DOTATOC is necessary to ensure the benefits outweigh its risks. University of Iowa Health Care PET Imaging Center submitted a New Drug Application (NDA) 210828 for Ga 68 DOTATOC with the proposed indication for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients (b) (4).[1] This application is under review in the DMIP. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Ga 68 DOTATOC, a new molecular entity, is a diagnostic radiopharmaceutical proposed for use with PET for localization of somatostatin receptor positive NETs in adult and pediatric patients (b) (4). Ga 68 DOTATOC is radiolabeled analogue of somatostatin with the chelator DOTA (gallium-68 DOTA-0-Phe1-Tyr3 octreotide). The approved radiolabeled analogue of somatostatin, gallium Ga 68 dotatate (Netspot), contains the positron emitter gallium-68, chelator DOTA, and octreotide derivative Tyr3-octreotate (gallium-68 DOTA-0-Tyr3-octreotate).[2345] Ga 68 DOTATOC binds to somatostatin receptors with a high affinity to subtype 2 receptors (sstr2). It is supplied as a 18.5 to 148 MBq/mL (0.5 to 4 mCi/mL) multiple dose vial for injection. The proposed dosing regimen in adults is 148 MBq (4 mCi) intravenous injection and in pediatrics is 1.59 MBq/kg (0.043 mCi/kg) with a range of 11.1 MBq (0.3 mCi)

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

up to 111 MBq (3 mCi) intravenous injection.[b] Ga 68 DOTATOC is not currently approved in any jurisdiction. Ga 68 DOTATOC was designated an orphan drug.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for Ga 68 DOTATOC NDA 210828 relevant to this review:

- 10/25/2013: Orphan drug designation granted
- 05/23/2018: NDA 210828 submission for use with PET for localization of somatostatin receptor positive NETs in adult and pediatric patients (b) (4) received
- 10/18/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Ga 68 DOTATOC

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Neuroendocrine tumors are malignancies that originate in the endocrine system.[6] Neuroendocrine tumors are located in the gastrointestinal tract, in the lungs, bronchi, thymus, and pancreas, and less commonly occur in the parathyroid, thyroid, adrenal, and pituitary glands. Patients with NET may have symptoms due to hormone and vasoactive peptide secretion.[67] The annual age adjusted incidence of NET from the Surveillance, Epidemiology, and End Results (SEER) program data in 2012 was 6.98 per 100,000 persons.[8c] Median overall survival for patients with NET was 9.3 years.[d] However, the median overall survival for localized, regional, and distant NETS was > 30 years, 10.2 years, and 12 months, respectively.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Imaging studies used to locate NET include CT, MRI, indium In 111 pentetreotide (Octreoscan), and gallium 68 somatostatin analogs.[5] Somatostatin analogs are used for imaging, as NET may overexpress somatostatin receptors.[56] Indium In 111 pentetreotide, a radiolabeled DTPA conjugate of octreotide, was approved by the FDA in 1994 for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.[9] Gallium Ga 68 dotatate was approved by the FDA in 2016 for use with PET for localization of somatostatin receptor positive NETs in adult and pediatric patients.[2] Adverse effects reported in clinical trials with indium In 111 pentetreotide (<1%)

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

included dizziness, fever, flushing, headache, hypotension, changes in liver enzymes, joint pain, nausea, sweating, and weakness.[9] No serious adverse reactions were observed with gallium Ga 68 dotatate in clinical studies.[2] Neither radiopharmaceutical agent has a boxed warning in their respective labels or have required a REMS for approval.

4 Benefit Assessment

The efficacy and safety of Ga 68 DOTATOC for use with PET for localization of somatostatin receptor positive NETs in adult and pediatric NET patients was demonstrated in the pivotal RET-NET-01 study.[10] RET-NET-01 was a retrospective study of three ongoing prospective open label studies at the University of Iowa. Study 1 (NCT 01619865) was a Phase 1/2 study in patients with known or suspected SSTR positive tumors, study 2 (NCT 01869725) was a Phase 2 study in patients with histologically proven NET or other SSTR positive tumors, and study 3 (NCT 02441062) was a Phase 2 study in patients with SSTR positive tumors. Study 1 and Study 2 were the pivotal efficacy studies in the RET-NET-01 study. The efficacy population consisted of subjects who participated in the prospective studies, received Ga 68 DOTATOC, and had sufficient data to establish NET status. The efficacy endpoint was positive percent agreement and negative percent agreement. Positive percent agreement was the proportion of patients positive for NET by composite reference of histopathology, imaging, and chromogranin A and pancreastatin levels identified positive by Ga 68 DOTATOC. Negative percent agreement was the proportion of patients without NET by composite reference of histopathology, imaging, and chromogranin A and pancreastatin levels identified negative by Ga 68 DOTATOC. Two independent readers reviewed the Ga 68 DOTATOC images.

In study 1 (n=184) the positive percent agreement was 90.5% (95% CI 84.3% to 94.9%) and the negative percent agreement was 89.4% (95% CI 76.9% to 96.5%) for reader 1. The positive percent agreement was 89.8% (95% CI 83.5% to 94.3%) and the negative percent agreement was 85.1% (95% CI 71.7% to 93.8%) for reader 2. In study 2 (n=59) the positive percent agreement was 92% (95% CI 80.8% to 97.8%) and the negative percent agreement was 75% (95% CI 34.9% to 96.8%) for reader 1. The positive percent agreement was 90.2% (95% CI 78.6% to 96.7%) and the negative percent agreement was 87.5% (95% CI 47.4% to 99.7%) for reader 2. Study 3 had a smaller efficacy analysis population (n=26) and was not included in the current proposed labeling.

The FDA clinical reviewer concluded that the trials support the efficacy of Ga 68 DOTATOC for localization of somatostatin receptor positive NETs.[e]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions[f]

The safety of Ga 68 DOTATOC was evaluated in a retrospective analysis from three prospective clinical studies (NCT 01619865, NCT 01869725, NCT 02441062) from the RET-NET-01 study. The RET-NET-01 study included 334 patients. Common adverse events that were reported in the RET-NET-01 study included nausea, flushing, headache, pruritis, diarrhea, and abdominal pain. However, no serious adverse events were reported in the RET-NET-01 study.[10]

The serious risk[g] associated with Ga 68 DOTATOC which include radiation risk and risk of image misinterpretation are summarized in the sections below. The warnings and precautions of radiation risk and risk of image misinterpretation are also listed in the gallium Ga 68 dotatate label.

5.1 Radiation Risk

Similar to other radiopharmaceuticals, Ga 68 DOTATOC adds to overall long-term cumulative radiation exposure. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 Risk for Image Misinterpretation

Uptake of Ga 68 DOTATOC may also be observed in other tumor types with somatostatin receptors, other pathologic conditions such as thyroid disease or subacute inflammation, or as a normal physiologic variant such as uncinate process of the pancreas. If approved, this risk will be communicated in the warnings and precautions section of the label.

6 Expected Postmarket Use

If approved, Ga 68 DOTATOC will be used in the inpatient setting.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Ga 68 DOTATOC beyond routine pharmacovigilance and labeling.

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[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of Ga 68 DOTATOC on the basis of the efficacy and safety information currently available. Ga 68 DOTATOC is a somatostatin analogue with acceptable positive percent agreement and negative percent agreement for localization of somatostatin receptor positive NET. The serious risk associated with Ga 68 DOTATOC of radiation risk and risk of image misinterpretation will be addressed in the warnings and precautions section of the label. No serious adverse events were reported in the RET-NET-01 study. DRISK recommends that a REMS is not necessary to ensure the benefits outweigh the risks of Ga 68 DOTATOC for use with PET for localization of somatostatin receptor positive NETs in adult and pediatric patients (b) (4). The radiopharmaceutical agents indium In 111 pentetreotide and gallium Ga 68 dotatate also do not have a boxed warning in their respective labels or have required a REMS for approval.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for Ga 68 DOTATOC to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

[1]Proposed prescribing information for Ga 68 DOTATOC injection as currently edited by FDA, Accessed 2/12/2019.

[2]Netspot (gallium Ga 68 dotatate) package insert. New York, NY: Advanced Accelerator Applications USA, Inc.; 2018 April.

[3]Pampaloni MH, Nardo L. PET/MRI radiotracer beyond ^{18}F-FDG. PET Clin. 2014;9(3):345-9.

[4]Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics. 2015;35(2):500-16.

[5]Yu R, Wachsman A. Imaging of neuroendocrine tumors: indications, interpretations, limits, and pitfalls. Endocrinol Metab Clin North Am. 2017;46(3):795-814.

[6]National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Neuroendocrine and adrenal tumors (version 4.2018 – January 7, 2019).

[7]Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011;29(7):934-43.

[8]Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335-1342.

[9]Octreoscan (Indium In 111 pentetreotide) package insert. Maryland Heights, MO: Curium US; 2018 December.

[10]Ga 68 DOTATOC multi-disciplinary review and evaluation. Accessed 2/14/2019.

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/s/

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I concur.

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