CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214511Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	214511
PDUFA Goal Date	November 17, 2023
Nexus TTT #	2023-4105
Reviewer Name	Stephanie Olumba, PharmD, MPH, BCPS
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 8, 2024
Subject	Evaluation of Need for a REMS
Established Name	Pegulicianine
Trade Name	Lumisight
Name of Applicant	Lumicell, Inc.
Therapeutic Class	Optical imaging agent
Formulation(s)	Lyophilized powder for reconstitution
Dosing Regimen	1 mg/kg by intravenous injection over 3 minutes administered 2 hours to 6 hours prior to imaging

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Lumisight (pegulicianine) is necessary to ensure the benefits outweigh its risks. Lumicell, Inc. (the Applicant) submitted a New Drug Application (NDA) 214511 for Lumisight with the proposed indication for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery. Lumisight is used with the Lumicell Direct Visualization System (DVS) for fluorescence imaging of the lumpectomy cavity. The risks associated with Lumisight are anaphylaxis and other serious hypersensitivity reactions, risk of misdiagnosis, and interference from dyes used for sentinel lymph node mapping. These risks will be communicated through labeling. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Lumisight outweigh its risks. Lumisight is a single dose expected to be administered preoperatively by a healthcare provider in a hospital or surgical center, which should have emergency resuscitation drugs, equipment, and healthcare providers available to manage the risk of anaphylaxis.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lumisight (pegulicianine) is necessary to ensure the benefits outweigh its risks. Lumicell, Inc. (hereafter referred to as the Applicant) submitted a new drug application (NDA) 214511 for Lumisight with the proposed indication for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery. This application is under review in the Division of Imaging and Radiation Medicine (DIRM). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Lumisight (pegulicianine), a new molecular entity,[a] is an optical imaging agent proposed for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery. Lumisight is used with the Lumicell Direct Visualization System (DVS) or other fluorescence imaging device that is FDA approved for specific use with Lumisight in the indicated population. Lumisight is a prodrug that is optically inactive when intact and produces a fluorescent signal after its peptide chain is cleaved by cathepsins and matrix metalloproteases. The levels of these enzymes are higher in and

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

around tumor and tumor associated cells than normal cells. The fluorescence signal from cleaved Lumisight is detected by the Lumicell DVS, which displays images on a computer screen of suspected tissue containing cancer within the lumpectomy cavity following removal of the primary specimen during lumpectomy surgery.

Lumisight is supplied as 39 mg of dark blue lyophilized powder for reconstitution.[1] The proposed dose is a single dose of 1 mg/kg actual body weight by intravenous injection over 3 minutes administered 2 hours to 6 hours prior to imaging. [b] It is expected that Lumisight will be administered preoperatively in a hospital or surgical center by a healthcare provider. Lumisight is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 214511 relevant to this review:

- **03/28/2018:** A Breakthrough Device designation was granted for the LUM Imaging System for use in patients undergoing breast conserving surgery for breast cancer.
- **10/29/2020:** Fast Track designation granted.
- **03/17/2023:** NDA 214511 submission for use in adults with breast cancer as an adjunct for the detection of cancerous tissue within the lumpectomy cavity following removal of the primary specimen during lumpectomy surgery received.
- **06/29/2023:** A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there were no specific major safety concerns and there is currently no plans for a REMS at this time, however the review is ongoing.
- **03/05/2024:** A Medical Imaging Drugs Advisory Committee Meeting was convened to discuss efficacy and safety data submitted in support of NDA 214511 for Lumisight. The AC voted 16 yes, 2 no, and 1 abstain that the benefits of Lumisight outweigh its risks.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Breast cancer is the most common cancer and the second leading cause of cancer death in women in the United States (US).[2] An estimate of 300,590 cases will be diagnosed with breast cancer in 2023 in the US, with approximately 43,700 deaths.[3] In early-stage breast cancer, patients have the surgical option of receiving lumpectomy surgery (i.e., breast-conserving surgery [BCS]), an alternative to mastectomy. In 2018, 63% of patients with stage I or II breast cancer underwent lumpectomy with or without adjuvant radiation therapy.[2,c] The main objective of lumpectomy is the complete removal of cancerous tissue surrounded by a margin of normal tissue while attaining a satisfactory cosmetic outcome. Survival outcomes after lumpectomy have been reported to be equivalent to mastectomy for women with early-

[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.*

stage disease.[4] The presence of cancer cells at the lumpectomy margins (i.e., positive margins) is a strong predictor of local recurrence, and may require an additional surgery (i.e., re-excision) to obtain negative margins. Approximately 20-40% of patients will have to undergo re-excision due to positive microscopic margins.[5] Re-excision is associated with greater morbidity, poorer cosmetic outcome, and increased medical cost; and thus, there is a need for improved intraoperative imaging tools to ensure clear margins at the time of the lumpectomy. [d]

3.2. Description of Current Treatment Options

There are currently no FDA-approved drugs or intraoperative technologies available that directly examines residual cancerous tissue within the lumpectomy cavity following removal of the primary specimen during lumpectomy surgery. Pathological evaluation of margin status is completed days after surgery, and patients that have positive margins with cancer cells will require re-excision surgery.[6]

Current intraoperative techniques to identify positive margins rely on ex-vivo specimen analysis, and include the use of radiofrequency spectroscopy (e.g., MarginProbe), specimen radiography, and optical coherence tomography.[7-9] Radiographic approaches are also used before lumpectomy to guide placement of a surgical wire or other marker to target the cancerous tissue for removal. There are no in vivo imaging products or modalities available to assist breast cancer surgeons in examining the lumpectomy cavity for a signal of residual cancer, which would facilitate excision of cancer that remained in situ during and after the initial surgery.

4. Benefit Assessment

The efficacy of Lumisight used with Lumicell DVS in identifying residual cancer in the lumpectomy cavity of female patients with breast cancer was evaluated through an adequate and well-controlled multicenter clinical trial (CL0007) plus the confirmatory evidence from a second multicenter study (CL0006). Study CL0007 was a prospective, multicenter, two-arm, randomized, blinded study which evaluated 392 female patients with breast cancer undergoing lumpectomy procedure for invasive breast cancer, ductal carcinoma in situ (DCIS), or both. Patients were excluded if they received neoadjuvant chemotherapy or radiotherapy prior to surgery, and if patients were scheduled for bilateral breast cancer resection, follow up surgery for positive margins from a prior lumpectomy, or a breast cancer surgery involving frozen section analysis. Patients were randomized at a 10:1 ratio to either image-directed surgery with the Lumicell DVS (device arm, n = 357) or no image-directed surgery (control arm, n = 35). All enrolled patients, regardless of randomization, received Lumisight 1 mg/kg intravenously at a surgical center or hospital 2 hours to 6 hours prior to surgery. After the surgery was completed, the entire lumpectomy cavity was scanned using the Lumicell DVS for subjects randomized to the device arm. For subjects with positive fluorescence signal detected, the tissue was resected with a cavity shave procedure. All subjects in both the device arm and the control arm received pathologic margin assessment of resected specimens after surgery per standard of care.

[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.*

The co-primary endpoints for study CL0007 were patient-level removal of residual cancer, defined as the fraction of patients who had cancer found in at least one therapeutic shave among all patients; tissue-level sensitivity; and tissue-level specificity. Tissue-level sensitivity and specificity were used to assess diagnostic performance of Lumisight and the Lumicell DVS. Secondary endpoints included patient-level sensitivity and specificity; volume of tissue removed by therapeutic shaves; contribution of therapeutic shave volume to total tissue removed; patient satisfaction survey results; and conversion rate, defined as the proportion of patients with pathology positive margins after standard of care (SoC) BCS for whom therapeutic shaves resulted in pathology negative margins among patients with positive margins after SoC BCS and among all patients.

The coprimary endpoint of patient-level removal of residual cancer met the prespecified performance goal of 3% of the lower bound of the 95% confidence interval (CI) (7.6%; (95% CI: 5.0%, 10.8%)). The coprimary endpoint of tissue-level sensitivity did not meet its prespecified performance goal of 40% of the lower bound of the 95% CI (49.1% (95% CI: 36.4%, 61.9%)), however, this threshold was not set based on the lowest clinically useful value. The coprimary endpoint of tissue-level specificity met its prespecified performance goal of 60% (86.5% (95% CI: 84.5%, 88.3%)).[10]

Study CL0006 was an open-label, single-arm (nonrandomized), multicenter clinical study undertaken to refine and verify the algorithm used for detection of residual cancer tissue. The primary endpoints of study CL0007 were applied to study CL0006 retrospectively. The results provided confirmatory evidence of effectiveness of Lumisight in detecting residual cancer and guiding the removal of the cancerous tissue. In the validation cohort, 9 of 103 patients had residual cancer confirmed by histopathology in at least one Lumisight-guided shave (9%; 4%, 16%).

The clinical review team concluded that data from study CL0007 and the confirmatory evidence from study CL0006 have provided evidence of effectiveness to support approval for Lumisight, when being used with Lumicell DVS, for the fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery. [10,e]

Refer to the Multidisciplinary Review and Evaluation: NDA 214511 Lumisight (pegulicianine) for more information.[10]

5. Risk Assessment & Safe-Use Conditions

The safety database included 790 subjects that were injected with Lumisight; this included 710 subjects with breast cancer, 56 subject with other cancers, and 24 healthy volunteers. Of the 790 subjects, 726 subjects with cancer received a single dose of Lumisight 1 mg/kg. The most common adverse event was chromaturia occurring in 85% of subjects, that typically resolved within 48 hours after administration with the longest time to resolution of 6 days. There were no deaths reported in the safety population.

[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.*

There were 8 subjects that experienced 9 adverse events leading to study discontinuation. The events leading to discontinuation were hypersensitivity (n=3), anaphylactic reaction (n=2), extravasation (n=2), skin discoloration (n= 1 coexisting with extravasation), and nausea (n=1).

There were 9 subjects that experienced a total of 11 serious adverse event in the overall safety population; of these, 4 serious adverse events were categorized to be related to Lumisight. These events were anaphylactic reaction (n=3) and hypersensitivity (n=1).

The warnings and precautions section of the labeling will describe the risk of anaphylaxis and other serious hypersensitivity reactions, risk of misdiagnosis, and interference from dyes used for sentinel lymph node mapping. [f]

5.1. Anaphylaxis and Other Serious Hypersensitivity Reactions

In clinical studies, hypersensitivity reactions occurred in 1.4% (10/726) of subjects, including anaphylaxis that occurred in 0.6% (4/726) of subjects. Three out of four subjects that experienced anaphylaxis did not have a history of hypersensitivity reaction to contrast media or products containing polyethylene glycol (PEG).

The risk will be communicated in labeling in a boxed warning and warnings and precautions. The label provides information for healthcare providers to prepare for the possibility of drug hypersensitivity reactions (including anaphylactic reactions) and how to take the necessary precautions. The label also states to always have emergency resuscitation drugs, equipment, and trained personnel available. Before Lumisight administration, healthcare providers are advised to assess all patients for any history of hypersensitivity reaction to contrast media or products containing PEG, as these patients may have an increased risk for hypersensitivity reaction to Lumisight. Healthcare providers are also advised to monitor all patients for hypersensitivity reactions using symptom reporting, direct observation, and vital sign measurements. If a hypersensitivity reaction is suspected, healthcare providers are advised to immediately discontinue Lumisight injection and initiate appropriate therapy.

5.2. Risk of Misdiagnosis

False positive and false negative findings may occur during use of Lumisight to detect residual cancer. The proposed labeling advises healthcare providers that the absence of signal in the lumpectomy cavity does not rule out the presence of residual cancer. Additionally, positive signal has been observed in some non-cancerous tissue.

[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.*

5.3. Interference from Dyes Used for Sentinel Lymph Node Mapping

The proposed label advises healthcare providers that blue dyes (b) (4) used for sentinel lymph node mapping procedures interfere with Lumisight and to avoid administration of blue dyes in patients who have received Lumisight.

6. Expected Postmarket Use

Lumisight is a single dose expected to be administered preoperatively in a hospital or surgical center by medical staff. The expected prescribers are breast cancer surgeons who should be able to recognize and manage the aforementioned risks.

7. Risk Management Activities Proposed by the Applicant

7.1. Other Proposed Risk Management Activities

At the time of this review, the review team has determined that a postmarketing requirement (PMR) is necessary for the Applicant to assess the incidence of anaphylactic reactions. The PMR will include a prospective observational study to evaluate incidence of anaphylactic reactions after administration of Lumisight. The study should assess adverse events (including laboratory data as needed), physical examination, assessment of blood pressure, heart rate, and oxygen saturation before and at multiple timepoints after Lumisight administration. The secondary study objective will be to evaluate the incidence of other serious of hypersensitivity reactions.

The review team has also recommended enhanced pharmacovigilance for hypersensitivity reactions, including anaphylaxis. Enhanced pharmacovigilance would not directly reduce the risk of hypersensitivity, but would foster more timely submission of hypersensitivity related safety information to FDA and may allow for a more rapid regulatory response if the observed reporting frequency, time to onset, or clinical severity of hypersensitivity reactions is greater than expected.[11]

Reviewer Comments: *We note that these other activities are outside of the scope of the REMS and defer to Division of Epidemiology and Pharmacovigilance for review and input.*

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of Lumisight on the basis of the efficacy and safety information currently available. Lumisight will be indicated for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.

The risks associated with Lumisight include anaphylaxis and other serious hypersensitivity reactions, risk of misdiagnosis, and interference from dyes used for sentinel lymph node mapping. The risk of

misdiagnosis (e.g., false positives and false negatives), as well as the risk of interference from dyes used for sentinel lymph node mapping will be communicated in the warnings and precautions of labeling.

The serious risks of anaphylaxis and other serious hypersensitivity reactions were of particular concern and these adverse events were discussed at the Medical Imaging Drugs Advisory Committee on March 5, 2024. When asked if the benefit of Lumisight outweighs its risks, 16 committee members voted yes, 3 voted no, and one abstained. A discussion on risk mitigation strategies under consideration was also held, and most members stated that a REMS was not needed to mitigate the risk of anaphylaxis associated with Lumisight. Lumisight is a single dose expected to be administered preoperatively in a hospital or surgical center by a healthcare provider. The proposed clinical settings are expected to be equipped with appropriate drugs, equipment, and healthcare providers who are available to diagnose, monitor, and manage these risks. Additionally, Lumisight's labeling will communicate the risk of anaphylaxis and other serious hypersensitivity reaction in a boxed warning.

This reviewer has determined that a REMS is not necessary to ensure the benefits of Lumisight outweigh the risks.

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary for Lumisight to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. References

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