CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761116Orig1s000

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	BLA
Application Number	761116
PDUFA Goal Date	December 21, 2018
OSE RCM #	2018-973; 2018-975
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	November 30, 2018
Subject	Review to determine if a REMS is necessary
Established Name	tagraxofusp-erzs
Trade Name	Elzonris
Name of Applicant	Stemline Therapeutics Inc.
Therapeutic Class	CD123-directed cytotoxin
Formulation(s)	1mg/mL in a single-use vial
Dosing Regimen	Administer tagraxofusp-erzs at 12µg/kg/day as an intravenous infusion over 15 minutes once daily on days 1-5 of a 21-day cycle.

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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 tagraxofusp-erzs (Elzonris) is necessary to ensure the benefits outweigh its risks. Stemline Therapeutics Inc. submitted a Biologic Licensing Application (BLA) 761116 for tagraxofusp-erzs with the proposed indication for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). The serious risks associated with the use of tagraxofusp-erzs are capillary leak syndrome (CLS), hypersensitivity reactions, and hepatotoxicity. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes a Boxed Warning, Warnings and Precautions, (b) (4)

DRISK and Division of Hematology Products (DHP) have determined that if approved, a REMS is not necessary to ensure the benefits of tagraxofusp-erzs outweigh its risks. BPDCN is a rare subtype of acute leukemia characterized by the clonal proliferation of precursors of plasmacytoid dendritic cells, also known as professional type I interferon-producing cells or plasmacytoid monocytes. Chemotherapy induction with acute lymphoblastic leukemia/lymphoma (ALL)-type regimens remains a mainstay for eligible patients. Despite these intensive therapies, the long-term prognosis for patients with BPDCN is poor. In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of BPDCN. The CR/CRc rate in the pivotal cohort was 54% and the median duration of CR/CRc was not reached with a median follow-up of 11.5 months. Tagraxofusp-erzs appeared efficacious in its primary outcomes. The most concerning adverse reactions observed with the use of tagraxofusp-erzs are CLS, hypersensitivity reactions, and hepatotoxicity. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of tagraxofusp-erzs for the treatment of patients with BPDCN in adults and in pediatric patients 2 years and older. Labeling, including a Boxed Warning, and Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with tagraxofusp-erzs.

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) tagraxofusp-erzs (Elzonris) is necessary to ensure the benefits outweigh its risks. Stemline Therapeutics Inc. submitted a Biologic Licensing Application (BLA) 761116 for tagraxofusp-erzs with the proposed indication for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).[1] This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Boxed Warning, Warnings and Precautions, (b) (4)

2 Background

2.1 PRODUCT INFORMATION

Tagraxofusp-erzs is a NME BLA type 351(a) pathway application.[a] It is a CD123-directed cytotoxin, with the proposed indication of treatment of patients with BPDCN. Tagraxofusp-erzs is constructed by recombinant DNA technology and produced in *Escherichia coli* cells. It is a recombinant fusion protein composed of human interleukin 3 (IL-3) and truncated diphtheria toxin (DT) that targets the interleukin-3 receptor (IL-3R/CD123) expressing cells. Tagraxofusp-erzs is prepared as 1mg/mL in a single-use vial to be administered intravenously. The recommended dose of tagraxofusp-erzs is 12 µg/kg/day as an intravenous infusion over 15 minutes once daily on days 1-5 of a 21-day cycle. The dosing period may be extended for dose delays up to day 10 of the cycle and continue treatment with tagraxofusp-erzs until disease progression or unacceptable toxicity.[b] Tagraxofusp-erzs was granted orphan drug designation on June 6, 2013, and breakthrough therapy designation on August 22, 2016. Tagraxofusp-erzs is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for tagraxofusp-erzs (BLA 761116) relevant to this review:

- 06/06/2013: Orphan Drug designation granted
- 06/27/2014: Investigation New Drug (IND) 114513 submission for SL-401 was received.
- 08/22/2016: Breakthrough therapy designation granted.
- 02/06/2018: Applicant informed at pre-BLA meeting that the need for a REMS for SL-401 will be made upon reviewing the BLA.
- 06/21/2018: BLA 761116 submission for tagraxofusp-erzs with the proposed indication for the treatment of patients with BPDCN, received.
- 10/03/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tagraxofusp-erzs.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

BPDCN is a rare subtype of acute leukemia characterized by the clonal proliferation of precursors of plasmacytoid dendritic cells, also known as professional type I interferon-producing cells or plasmacytoid monocytes. It is believed to arise from the plasmacytoid dendritic cell. The pathogenesis of

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

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

BPDCN is not well understood, although the neoplasm demonstrates frequent deletion of tumor suppressor genes, including RB1, CDKN1B, CDKN2A, and TP53. It is characterized by enhanced expression of CD56, CD4, and CD123, which can be detected by flow cytometry/immunohistochemistry.[2] The few available data reported indicate that its overall incidence is extremely low, accounting for 0.44% of all hematologic malignancies and 0.7% of cutaneous lymphomas.[3] Moreover, the leukemic form of disease is a rare phenomenon, representing <1% of cases of acute leukemia.[4] In a recent analysis based on Surveillance Epidemiology and End Results (SEER) data, the incidence of BPDCN in the USA is estimated to be 0.04 cases per 100,000 individuals[c], most of whom are Caucasian. Men are affected more commonly than women. Although the disease has been reported in all age groups, the median age of patients at diagnosis is 53 years.[5] Per the Orphanet encyclopedia, BPDCN is classified as a rare disease (Orphanet code ORPHA86870; ICD-10 code C86.4). A rare disease is defined therein as a disease with an estimated prevalence of 1-5/10,000 or less.[6,c] Cutaneous lesions are often the presenting sign for patients with BPDCN, identified in at least 64% of patients.[7] Other common sites of disease involvement include the bone marrow and lymph nodes, and some patients have an overtly leukemic presentation without discernible extramedullary disease at presentation.[8] Despite the frequent appearance of a somewhat indolent clinical presentation at the outset, the course of BPDCN is highly aggressive, and the median survival is approximately 8 to 14 months.[9,d] The disease almost always results in a terminal leukemic phase with proliferation of BPDCN blasts in the bone marrow and peripheral blood, leading to decreased blood cell counts with resultant infections, bleeding, and invariably death.[10,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Although the initial presentation of cutaneous lesions may appear to be indolent, BPDCN is a highly aggressive malignancy with rapid systemic dissemination for which no consensus therapy guidelines are yet available. Accordingly, patients who are diagnosed with BPDCN should be referred for treatment under a clinical trial if feasible. Patients diagnosed with BPDCN have more treatment options today than they did just a few years ago. Chemotherapy induction with acute lymphoblastic leukemia/lymphoma (ALL)-type regimens remains a mainstay for eligible patients, while allogeneic SCT offers the best chance for durable remission. Acute myeloid leukemia (AML)-type therapy may be associated with a worse outcome than acute lymphoblastic leukemia type therapy, in spite of evidence of closer biologic relatedness between plasmacytoid dendritic cells (PDCs) and the myeloid lineage.[11] At present, there is no standard therapy for BPDCN, and most published studies are based on retrospective data.[8] Lymphoma regimens including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CHEOP (CHOP plus etoposide) as well as ALL regimens such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and methotrexate and cytarabine) and GIMEMA ALL trial therapy (doxorubicin, vincristine, prednisone, asparaginase), with intrathecal therapy, were associated with significantly better overall survival results compared to acute myeloid leukemia regimens such as MICE (mitoxantrone, cytarabine, etoposide) or ICE (idarubicin, cytarabine, etoposide) for patients with BPDCN. Nonetheless, without stem cell transplant therapy (SCT) the median overall survival is generally dismal.[12,13] SCT, particularly allogeneic SCT, administered during first remission remains the only therapeutic modality that results in durable remissions.[8] However, despite these

[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.*

intensive therapies, median overall survival for adults with BPDCN, as reported by many groups, remains approximately 8–14 months; there is a clear need for new treatments for patients with BPDCN.

4 Benefit Assessment

The efficacy of tagraxofusp-erzs was evaluated in a multicenter, open-label, single-arm, clinical trial (STML-401-0114; NCT 02113982 [Study 0114]). The study population included 13 patients with untreated (first-line) BPDCN in the pivotal phase of the study and 15 patients with relapsed or refractory (R/R) BPDCN. Treatment consisted of ELZONRIS 12 mcg/kg on days 1 to 5 of each 21-day cycle.

The following section is a summary of relevant efficacy information to date for tagraxofusp-erzs. The efficacy in patients with treatment-naive BPDCN was established on the basis of the rate of complete response/clinical complete response (CR/CRc). Key secondary objectives included determining the duration of response, progression-free survival (PFS), and overall survival (OS) in subjects with BPDCN (pooled) as well as characterizing the pharmacokinetics and immunogenicity of tagraxofusp-erzs. The median time to CR/CRc was 57 days (range: 14 to 107). The efficacy results are shown in Table 1.[1,14,e] The CR/CRc rate in the pivotal cohort was 54% (95% CI: 25, 81), and the median duration of CR/CRc was not reached with a median follow-up of 11.5 months (95% CI: 8.8, 11.9). As such, the primary efficacy endpoint was met.[14,e]

Table 1. Efficacy Measures in Patients with Treatment-Naive BPDCN[1,14,e]

Parameter	Treatment-naive BPDCN
	Pivotal Phase **N=13**
CR/CRc* Rate, N (%) (95% CI)	7 (53.8) (25.1, 80.8)
Duration of CR/CRc (months) Median Minimum, Maximum	 Not Reached 3.9, 12.2
Duration of follow up (months) Median (95% CI)	 11.5 (8.8, 11.9)
* CRc is defined as complete response with residual skin abnormality not indicative of active disease.	

In the 15 patients with relapsed/refractory BPDCN, one patient achieved a CR (duration: 111 days) and one patient achieved a CRc (duration: 424 days).

5 Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for tagraxofusp-erzs. The safety analysis of tagraxofusp-erzs primarily focuses on a single-arm clinical trial with tagraxofusp-erzs in patients with newly-diagnosed or relapsed/refractory myeloid malignancies, in which a total of 94 patients received multi-cycle treatment with 12 mcg/kg of tagraxofusp-erzs monotherapy, including 58

[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.*

patients with BPDCN.[1] The 60-day safety update data set was also used for the safety analyses; therefore, the integrated summary of safety (ISS) pool has a total of 139 patients including dose-escalation studies from 7, 9, 12 or 16 mcg/kg of tagraxofusp-erzs doses for patients with myeloid malignancies (BPDCN (first-line and R/R; n=61), AML (n=49), and myeloproliferative neoplasms [MPN; n=29]).[14]

Deaths

FDA identified 85 deaths among 155 subjects exposed to tagraxofusp-erzs monotherapy. Most deaths occurred more than 30 days after the last dose of tagraxofusp-erzs (81%). Of the 16 on-treatment deaths, the applicant-reported causes of death were primary disease (n=6), fatal ARs (n=7) including capillary leak syndrome, MI, and sepsis/infection, or other intercurrent ARs (n=3). FDA agreed with the Sponsor's assessment of causality for most deaths except for 3 subjects, which are analyzed as CLS related Grade 5 events.

Serious Adverse Events (SAE)

The most common adverse reactions (all grades incidence ≥ 30%) are nausea (50%), fatigue (46%), peripheral edema (43%), pyrexia (46%), weight increase (31%), and headache (30%). Most common laboratory abnormalities (all grades incidence ≥ 50%) are decreases in albumin (77%), platelets (68%), hemoglobin (60%), calcium (57%), and sodium (52%), and increases in glucose (89%), alanine aminotransferase (ALT; 82%) and aspartate aminotransferase (AST; 79%).[1] Overall, 56% (78/139) of treated subjects had a dose delay or permanent discontinuation, including 59% (36/61) of the subjects in the BPDCN subgroup. Forty five percent (63/139) in the pool group and 54% (33/61) of patients in the BPDCN subgroup had a treatment delay and 11% (15/139) and 5% (3/61) of patients had a treatment withdrawal from the total pool group and BPDCN subgroup, respectively. The most common TEAE resulting in treatment delay in the BPDCN subgroup are elevated LFTs (26%; 16/21), pyrexia (11%; 7/61), CLS/infusion reaction (8%; 5/61), arrhythmia (3%; 2/61) and CLS signs/symptoms (44%; 27/61, which included weight increased (25%; 15/61), hypoalbuminemia (13%; 8/61), CLS (7%; 4/61), hypotension (3%; 2/61), and infusion related reactions (3%; 2/61). The most common TEAE resulting in permanent discontinuation in the BPDCN subgroup are elevated LFTs (3%; 2/61) and CLS signs/symptoms (2%; 1/61).[14]

If approved, labeling will include the following risks in the Warnings and Precautions section, as well as a Boxed Warning for CLS.

5.1 CAPILLARY LEAK SYNDROME (CLS)

In the clinical trial, CLS, including life-threatening and fatal cases, was reported in patients treated with tagraxofusp-erzs. The overall incidence of CLS, which is defined as the onset of 2 or more signs and symptoms of CLS within 7 days of each other, was 55% (52/94), including Grade 1 or 2 in 46% (43/94), Grade 3 in 6% (6/94), Grade 4 in 1% (1/94) and 2 fatal events (2/94, 2%) in patients receiving tagraxofusp-erzs in clinical trials.[f] Common signs and symptoms (incidence ≥ 20%) associated with CLS

[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.*

that were reported during treatment with tagraxofusp-erzs include hypoalbuminemia, edema, weight gain, and hypotension. If approved, labeling will instruct that prescribers ensure that the patient has adequate cardiac function and serum albumin ≥ 3.2 g/dL before initiating therapy with tagraxofusp-erzs. Additionally, labeling will recommend monitoring of serum albumin levels prior to the initiation of each dose of tagraxofusp-erzs, or more often as clinically indicated, and assessing patients for other signs or symptoms of CLS, which include weight gain, new onset or worsening edema, including pulmonary edema, and hypotension (b) (4) hemodynamic instability (b) (4).[1]

If approved, the risk of CLS will be included in the label as a Boxed Warning and in Warnings and Precautions. Management of CLS, including recommendations for initiating albumin and serum albumin monitoring and intravenous steroids, will be included in the Dosage and Administration section of the label to increase the prominence of this information and promote mitigation of CLS.

5.2 HYPERSENSITIVITY REACTIONS

In the clinical trial, events of hypersensitivity were reported in 46% (43/94) of patients treated with tagraxofusp-erzs and were (b) (4) Grade ≥ 3 (b) (4) in 10% (9/94) (b) (4).[1] Besides being communicated in the Warnings and Precautions section of the label, the label will also include a statement to premedicate patients with H1/H2-histamine antagonists and corticosteroids prior to each infusion. This section also instructs to observe patients for a minimum of 4 hours following each infusion.

5.3 HEPATOTOXICITY

In the clinical trial, elevations in liver enzymes were reported in 88% (83/94) of patients treated with tagraxofusp-erzs, and Grade ≥ 3 events were reported in 40% (38/94) of patients. Transient elevations in liver enzymes that are associated with treatment with tagraxofusp-erzs, largely occurring during the first cycle of therapy. If approved, labeling will recommend prescribers monitor ALT and AST prior to the initiation of each dose of tagraxofusp-erzs, and to withhold tagraxofusp-erzs temporarily if the transaminases rise to greater than 5 times the upper limit of normal, resuming treatment upon normalization or when (b) (4) resolved.[1] Besides being communicated in the Warnings and Precautions section of the label, recommended guidance for monitoring ALT and AST prior to the initiation of each dose of tagraxofusp-erzs will be communicated in the Dosage and Administration section of the label.

6 Expected Postmarket Use

The proposed indication is for the treatment of patients with BPDCN. It is expected that tagraxofusp-erzs will primarily be prescribed in the inpatient and outpatient ambulatory care settings and the likely prescribers will be oncologists/hematologists. The proposed label addresses the associated serious risks of tagraxofusp-erzs and their management with a Boxed Warning and in Warnings and Precautions. Recommendations for pretreatment medications, monitoring, and recommendations for withholding and/or discontinuing treatment will be included in the label.

7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application but proposed Prescribing Information that includes a Boxed Warning, Warnings and Precautions, (b) (4)

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for tagraxofusp-erzs, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The likely prescribers for tagraxofusp-erzs will be oncologists/hematologists, who will be informed about the risks associated with tagraxofusp-erzs treatment through labeling. It will be prescribed primarily in in the inpatient and outpatient ambulatory care settings.

Tagraxofusp-erzs is a CD123-directed cytotoxin, proposed for indication as treatment of patients with BPDCN. At the time of this writing, labeling negotiations were still ongoing with the Applicant. Based on the efficacy and safety information currently available, the clinical reviewers stated that tagraxofusp-erzs shows clinical meaningful benefit to patients with BPDCN, and recommends approval of tagraxofusp-erzs for the treatment of patients with BPDCN in adults and in pediatric patients 2 years and older.[14,g]

DRISK and DHP have determined that if approved, a REMS is not necessary to ensure the benefits of tagraxofusp-erzs outweigh its risks. Labeling, including a Boxed Warning, and Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with tagraxofusp-erzs. The most concerning adverse reactions observed with the use of tagraxofusp-erzs are CLS, hypersensitivity reactions and hepatotoxcity. Tagraxofusp-erzs appeared efficacious in its primary outcomes and its risks will be communicated through labeling. Chemotherapy induction with acute lymphoblastic leukemia/lymphoma (ALL)-type regimens remains a mainstay for eligible patients. Despite these intensive therapies, the long-term prognosis for patients with BPDCN is poor. In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of BPDCN.

Similar to moxetumomab pasudotox (Lumoxiti)[15], CD22-directed cytotoxin, the sponsor has proposed labeling that includes the risk of CLS as a Boxed Warning and Warning and Precautions and recommendations for the management of CLS are included in the Warnings and Precautions and Dosage and Administration sections of the label. The risks of hypersensitivity reactions and hepatotoxicity will likely be in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with tagraxofusp-erzs will be included in the Dosage and Administration section of the label. Since tagraxofusp-erzs will be prescribed primarily in in the inpatient

[g] Labeling negotiations were ongoing at the time of completion of this review. Indication statement is updated and significant changes to the proposed label made by FDA prior to negotiations.

and outpatient ambulatory care settings and provided under the care of a prescriber a Medication Guide (MG) will not be included as part of labeling.[h]

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of tagraxofusp-erzs. The management of the risks associated with tagraxofusp-erzs treatment will be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

[1] Draft Prescribing Information for tagraxofusp-erzs as currently edited by the FDA, last updated November 29, 2018.
[2] Shi Y, Wang E. Blastic plasmacytoid dendritic cell neoplasm: a clinicopathologic review. *Arch Pathol Lab Med.* 2014;138(4):564-569.
[3] Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica.* 2013;98(2):239-246.
[4] Jacob MC, Chaperot L, Mossuz P, et al. CD4+ CD56+ lineage negative malignancies: a new entity developed from malignant early plasmacytoid dendritic cells. *Haematologica.* 2003;88(8):941-955.
[5] Guru Murthy GS, Pemmaraju N, Atallah E. Epidemiology and survival of blastic plasmacytoid dendritic cell neoplasm. *Leuk Res.* 2018;73:21-23.
[6] Orphanet. The portal for rare diseases and orphan drugs. "CD4+/CD56+ hematodermic neoplasm." http://www.orpha.net/consor/cgi-bin/index.php. Accessed November 19, 2018.
[7] Martin-Martin L, Lopez A, Vidriales B, et al. Classification and clinical behavior of blastic plasmacytoid dendritic cell neoplasms according to their maturation-associated immunophenotypic profile. *Oncotarget.* 2015;6(22):19204-19216.
[8] Khoury JD. Blastic Plasmacytoid Dendritic Cell Neoplasm. *Curr Hematol Malig Rep.* 2018.
[9] Pemmaraju N. Novel Pathways and Potential Therapeutic Strategies for Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN): CD123 and Beyond. *Curr Hematol Malig Rep.* 2017;12(6):510-512.
[10] Stemline Therapeutics Inc. Clinical Overview for tagraxofusp-erzs,, dated June 21, 2018.
[11] Jegalian AG, Facchetti F, Jaffe ES. Plasmacytoid dendritic cells: physiologic roles and pathologic states. *Adv Anat Pathol.* 2009;16(6):392-404.
[12] Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica.* 2013;98(2):239-246.
[13] Martin-Martin L, Almeida J, Pomares H, et al. Blastic plasmacytoid dendritic cell neoplasm frequently shows occult central nervous system involvement at diagnosis and benefits from intrathecal therapy. *Oncotarget.* 2016;7(9):10174-10181.
[14] Jen E. DHP Clinical Review for BLA 761116 tagraxofusp-erzs, dated November 23, 2018.
[15] Lumoxiti. Prescribing Information (last updated 09/2018)

[h] Jen E to Olickal T. (Internal communication from clinical reviewer to DRISK), dated November 20,2018.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
11/30/2018

ELIZABETH E EVERHART
11/30/2018
I concur.

CYNTHIA L LACIVITA
11/30/2018