CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761104Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<td><strong>PDUFA Goal Date</strong></td>
<td>September 29, 2018</td>
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<td><strong>Reviewer Name(s)</strong></td>
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<td><strong>Review Completion Date</strong></td>
<td>July 2, 2018</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>Moxetumomab pasudotox</td>
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<td><strong>Trade Name</strong></td>
<td>Lumoxiti</td>
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<tr>
<td><strong>Name of Applicant</strong></td>
<td>AstraZeneca</td>
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<td><strong>Therapeutic Class</strong></td>
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<td><strong>Formulation(s)</strong></td>
<td>1 mg vial of lyophilized powder and 1 mL vial of IV solution stabilizer</td>
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<td><strong>Dosing Regimen</strong></td>
<td>0.04 mg/kg IV over 30 minutes on Days 1, 3, and 5 of each 28-day cycle</td>
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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 (NME) Lumoxiti (moxetumomab pasudotox) is necessary to ensure the benefits outweigh its risks. AstraZeneca submitted a Biologics License Application (BLA 761104) for moxetumomab pasudotox with the proposed indication for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog. The serious risks associated with moxetumomab pasudotox are hemolytic uremic syndrome, capillary leak syndrome, renal toxicity, infusion reactions, electrolyte abnormalities, (b)(4). The applicant did not submit a proposed REMS or risk management plan with this application.

If moxetumomab pasudotox is approved, labeling will communicate the associated serious risks and their management. Hemolytic uremic syndrome and capillary leak syndrome will be addressed with a Boxed Warning. The Warnings and Precautions section of the proposed label will address the risks of renal toxicity, infusion reactions, electrolyte abnormalities, (b)(4). The likely prescribers of moxetumomab pasudotox will be hematologists. The labeling will include recommendations for pre-treatment hydration, post-treatment medications, monitoring, and recommendations for withholding and/or discontinuing treatment. DRISK and the Division of Hematology Products (DHP) agree that a REMS is not needed to ensure the benefits of moxetumomab pasudotox outweigh its risks for the proposed indication: for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog.

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) Lumoxiti (moxetumomab pasudotox) is necessary to ensure the benefits outweigh its risks. AstraZeneca submitted a Biologics License Application (BLA 761104) for moxetumomab pasudotox with the proposed indication for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA). This application is under review in the Division of Hematology Products. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information
Lumoxiti (moxetumomab pasudotox), a new molecular entity, is CD22-directed cytotoxin proposed for treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a PNA. Moxetumomab pasudotox is proposed as a (b)(4) mg single dose vial of lyophilized powder (requires reconstitution) and a 1 mL single dose vial of intravenous (IV) solution stabilizer. The recommended dose is 0.04 mg/kg IV on Days 1, 3, and 5 of
each 28-day cycle. Treatment is continued until a maximum of 6 cycles, disease progression, or unacceptable toxicity.\textsuperscript{1} Moxetumomab pasudotox is not currently approved in any jurisdiction.

\section*{2.2 Regulatory History}
The following is a summary of the regulatory history for BLA 761104 relevant to this review:

- 11/30/2017: BLA 761104 submission for the treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analog received
- 05/02/2018: 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 moxetumomab pasudotox

\section*{3 Therapeutic Context and Treatment Options}

\subsection*{3.1 Description of the Medical Condition}
Hairy cell leukemia (HCL) is a chronic lymphoid leukemia that represents 2\% of all leukemia cases. An estimated 1100 new cases were diagnosed in the United States in 2016.\textsuperscript{2a} HCL is four to five times more common in males than in females with a median age of 49-51 years.\textsuperscript{3} People with HCL may present with weakness, fatigue, abdominal discomfort, pancytopenia and splenomegaly. Weight loss, fever, and night sweats may also occur.\textsuperscript{b} With appropriate treatment, the 5-year survival of those with HCL ranged from 84\% - 94\% in the U.S.\textsuperscript{2}

\subsection*{3.2 Description of Current Treatment Options}
Non-pharmacologic treatment of HCL includes a watch and wait approach that necessitates quarterly blood cell counts and physical exams (at a minimum). Once symptoms are present or blood counts decline, treatment is initiated with a purine analogue. The purine analogues indicated to treat HCL are cladribine and pentostatin. Treatment with cladribine or pentostatin should be discontinued once complete remission or stable partial remission occurs.\textsuperscript{4} Minimal residual disease can be found in a very high percentage of patients treated with nucleoside analogues.\textsuperscript{5} Those with relapsing/refractory HCL are often successfully retreated with cladribine or pentostatin. Rituximab may also be used in combination or sequentially with cladribine or pentostatin in relapsed/refractory HCL. Interferon-alpha and splenectomy are therapeutic options that can be considered when other options have been exhausted.\textsuperscript{4} All currently available therapies for HCL have Boxed Warnings in their respective labels. See table 1 in the appendix for additional details.

\textsuperscript{a} Section 505-1 (a) of the FD&C Act: \textit{FDAAA factor (A): The estimated size of the population likely to use the drug involved.}

\textsuperscript{b} Section 505-1 (a) of the FD&C Act: \textit{FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.}
4 Benefit Assessment

The efficacy and safety of moxetumomab pasudotox for the treatment of HCL was demonstrated in two studies. Both studies enrolled patients who were 18 years or older with relapsed or refractory HCL.

Study CD-ON-CAT-8015-1053 (referred to as Study 1053; NCT01829711) was a pivotal, Phase 3, multicenter, open-label, single-arm study in 80 patients (treated: n = 63) who received at least 2 prior systemic therapies, including 2 lines of PNA or 1 line of either rituximab or BRAF inhibitor, following a single prior line of PNA. The dosing regimen for moxetumomab pasudotox was 0.04 mg/kg IV on Days 1, 3, and 5 of each 28-day cycle. Treatment was continued until documentation of complete response (CR) with MRD negativity or for a maximum of 6 cycles, or until disease progression, unacceptable toxicity, or initiation of alternate therapy. The primary efficacy endpoint was the rate of durable CR as defined by blinded independent central review (BICR). Durable CR was defined as hematologic remission lasting >180 days. The BICR-assessed durable CR rate was 30.0% (24/80 patients; 95% CI: 20.3%, 41.3%).

Study CAT-8015-1001 (referred to as Study 1001; NCT00586924) was a supportive, Phase 1, multicenter, open-label, dose-escalation and dose-expansion study in 49 patients who received at least 2 prior lines of PNA, or 1 line of PNA if the disease response lasted < 2 years or if the patient had unacceptable toxicity to PNA. The dosing regimen for moxetumomab pasudotox was either 0.005 mg/kg (n = 3), 0.01 mg/kg (n = 3), 0.02 mg/kg (n = 3), 0.03 mg/kg (n = 3), 0.04 mg/kg (n = 4), or 0.05 mg/kg (n = 33) IV on Days 1, 3, and 5 of each 28-day cycle. The primary efficacy endpoint was investigator-reported per protocol assessments of antitumor activity which included best overall response (BOR), objective response rate (ORR), time to response, duration of response, time to progression/relapse, and progression-free survival. The ORR in the overall population was 85.7% (42/49; 95% CI: 72.8%, 94.1%).

The median time to achieving a CR was 3.6 months (95% CI, 2.69, 5.22) and the median duration of CR was 70.34 months (95% CI: 19.09, not estimable). The median time to OR (normalization of hematologic parameters) was 1.15 months (95% CI: 1.02, 1.87) and the median duration of OR was 80.95 months, with loss of CR or PR occurring in 23.8% of patients overall. During follow-up, 10 of 49 patients (20.4%) relapsed, developed progressive disease, or died because of their disease. The PFS rate at 1 year was 88% (95% CI:74%, 95%).

The statistics reviewer concluded that the durable CR per BICR satisfies the applicant’s definition of “compelling efficacy” results. The clinical reviewer recommends regular approval of moxetumomab pasudotox as durable response represents an endpoint of meaningful clinical benefit.

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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

The safety and tolerability of moxetumomab pasudotox was assessed from the results of 5 sponsored studies in 165 patients. This includes the pivotal study 1053 and the supportive study 1001 discussed previously in the benefit assessment. The 3 additional studies are studies CAT-8015-1002 (study 1002; NCT00587457), CAT-8015-1003 (study 1003; NCT00587015), and MI-CP218 (study CP218; NCT01030536). Study 1002 was a Phase 1, open-label, single arm, dose-escalation study in patients with relapsed or refractory B-cell leukemia. Study 1003 was a Phase 1, open-label, single arm, dose-escalation study in patients with non-Hodgkin lymphoma. Study CP218 was a Phase 1/2 open-label, single arm, dose-escalation and expanded cohort study in patients with relapsed or refractory B-cell chronic lymphocytic leukemia or non-Hodgkin lymphoma. The safety population was assessed in the following 3 groups:

1. **Primary HCL Population (n = 129):** This is the target population and included studies 1053 and 1001. This population consists of all patients in the 2 HCL studies who have received at least 1 dose of moxetumomab pasudotox at any dose level.

2. **Pivotal HCL Population (n = 80):** This population consists of all patients in the pivotal Phase 3 study who received at least 1 dose of moxetumomab pasudotox.

3. **Adult Population (n = 165):** This population consists of all patients in the pooled adult studies who have received at least 1 dose of moxetumomab pasudotox at various dose levels, treatment durations, and across multiple hematologic malignancy indications.

The serious adverse reactions (referred to as risks) determined to be associated with moxetumomab pasudotox are hemolytic uremic syndrome, capillary leak syndrome, renal toxicity, infusion reactions, electrolyte abnormalities, etc. These risks and the deaths that occurred are discussed below.

### 5.1 **Hemolytic Uremic Syndrome**

Adverse events of HUS included events of HUS, HUS-like syndrome and thrombotic microangiopathy (TMA). Overall, treatment-emergent adverse events (TEAEs) of HUS were reported in 20/165 (12.1%) patients in the adult population with 12 (7.3%) being CTCAE (Common Terminology Criteria for Adverse Events) Grade 3 or above. Of these, 19/129 (14.7%) were in the primary HCL population and 9/80 (11.3%) were in the pivotal HCL population. The proposed label addresses HUS with a Boxed Warning. The Warnings and Precautions section of the label addresses HUS with recommendations to administer...
required hydration and monitor platelet count, hemoglobin, and creatinine levels prior to each infusion and as clinically indicated. Warnings and Precautions (b)(4) discontinue moxetumomab pasudotox.

5.2 Capillary Leak Syndrome
Overall, TEAEs of capillary leak syndrome (CLS) were reported in 64/165 (38.8%) patients in the adult population with 6 (3.6%) being CTCAE Grade 3 or above. Of these, 52/129 (40.3%) were in the primary HCL population and 20/80 (25%) were in the pivotal HCL population. One CTCAE Grade 5 fatal event occurred. The Grade 5 CLS adverse event was documented as due to acute respiratory distress syndrome and dyspnea. The proposed label addresses CLS with a Boxed Warning. The Warnings and Precautions section of the label addresses CLS with recommendations to monitor patient weight and blood pressure prior to each infusion and regularly during treatment. Warnings and Precautions also recommends, depending on severity to delay dosing or discontinue moxetumomab pasudotox.

5.3 Renal Toxicity
Overall, TEAEs of renal toxicity were reported in 51/165 (30.9%) patients in the adult population with 5 (3%) being CTCAE Grade 3 or above. Of these, 42/129 (32.6%) were in the primary HCL population and 19/80 (23.8%) were in the pivotal HCL population. The proposed label addresses renal toxicity in the Warnings and Precautions section with recommendations to monitor for changes in renal function prior to each infusion and as clinically indicated and to delay dosing until recovery.

5.4 Infusion Reactions
Overall, TEAEs of infusion reactions were reported in 106/165 (64.2%) patients in the adult population with 8 (4.8%) being CTCAE Grade 3 or above. Of these, 96/129 (74.4%) were in the primary HCL population and 62/80 (77.5%) were in the pivotal HCL population. The proposed label addresses infusion reactions in the Warnings and Precautions section.

5.6 Electrolyte Abnormalities
Overall, TEAEs of electrolyte abnormalities were reported in 88/165 (53.3%) patients in the adult population with 23 (13.9%) being CTCAE Grade 3 or above. Of these, 76/129 (56.6%) were in the primary HCL population and 37/80 (46.3%) were in the pivotal HCL population. The proposed label addresses electrolyte abnormalities in the Warnings and Precautions section.

5.7 Deaths
Overall, 20/165 (12.1%) deaths were reported in the adult population with 8/129 (6.2%) occurring in the primary HCL population and 4/80 (5%) occurring in the pivotal HCL population. Of the 20 deaths that occurred, 13 were due to study disease. Fatal adverse events (CTCAE Grade 5) occurred in 7/20 patients. The adverse events included pneumonia (n = 3), septic shock (n = 1), diffuse large B-cell
lymphoma (n = 1), acute respiratory distress syndrome (n = 1), and glioblastoma (n = 1). The FDA could not clearly exclude CLS symptoms as a related cause of death for 2 patients whose fatal adverse events were attributed to pneumonia and septic shock by the applicant.

### 6 Expected Postmarket Use

Moxetumomab pasudotox will be primarily prescribed in the outpatient infusion center setting and the likely prescribers will be hematologists. The proposed label addresses the associated serious risks of moxetumomab pasudotox and their management with a Boxed Warning and in Warnings and Precautions. The following instructions are incorporated in the proposed label: recommendations for pretreatment hydration, post treatment medications, monitoring and recommendations for withholding and/or discontinuing treatment.

### 7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for moxetumomab pasudotox.

### 8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of moxetumomab based on the efficacy and safety information currently available. HCL is a serious disease that that represents 2% of all leukemia cases. Approximately, 1000 new cases will be diagnosed every year. The standard treatment for relapsed/refractory HCL is with the purine analogues cladribine and pentostatin and often results in minimal residual disease that necessitates retreatment. Treatment with moxetumomab pasudotox offers an alternative for patients with relapsed/refractory HCL who have received at least two prior systemic therapies, including treatment with a PNA.

The serious risks associated with moxetumomab pasudotox include HUS, CLS, renal toxicity, infusion reactions, electrolyte abnormalities, and other conditions. These risks are addressed in the proposed label via a Boxed Warnings and Warnings and Precautions.

DRISK recommends that, should moxetumomab pasudotox be approved, a REMS is not necessary to ensure its benefits outweigh its risks for the treatment of relapsed/refractory HCL. The management of the serious risks of moxetumomab pasudotox will be described in the product label.

### 9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable and therefore, a REMS is not necessary for moxetumomab pasudotox 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


10.2 Table 1: Pharmacologic Treatment Options for Hairy Cell Leukemia10

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<th>Established name</th>
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<th>Risk Management Approaches</th>
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<td>Pentostatin injection (2'-deoxycoformycin; DCF)</td>
<td>Renal toxicity (dose-limiting) Liver toxicity (dose-limiting) Pulmonary toxicity (dose-limiting), Pulmonary toxicity, including fatal if used in combination with fludarabine phosphate Central nervous system toxicity (dose-limiting)</td>
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<td>Cladribine injection (2-Chlorodeoxyadenosine; CdA)</td>
<td>Neurological toxicity including irreversible paraparesis and quadraparesis Acute nephrotoxicity</td>
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<td>Interferon-Alfa-2b injection (Intron)</td>
<td>Alpha interferons, including interferon alfa-2b, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.</td>
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<td>Rituximab injection (Rituxan)</td>
<td>Infusion reactions Mucocutaneous reactions Hepatitis B virus reactivation Progressive multifocal leukoencephalopathy</td>
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/s/

INGRID N CHAPMAN
07/02/2018

CYNTHIA L LACIVITA
07/02/2018

concur