

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761051Orig1s000

**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	761051
PDUFA Goal Date	June 4, 2018 (Goal action date March 23, 2018)
OSE RCM #	2017-2042
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 4, 2018
Subject	Evaluation of Need for a REMS
Established Name	Mogamulizumab
Trade Name	Poteligeo
Name of Applicant	Kyowa Kirin Pharmaceutical Development, Inc.
Therapeutic Class	Recombinant humanized monoclonal antibody
Formulation(s)	Intravenous infusion
Dosing Regimen	1 mg/kg on days 1, 8, 15, 22 of first 28-day cycle, and days 1 and 15 of subsequent cycles

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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 Poteligeo (mogamulizumab) is necessary to ensure the benefits outweigh its risks. Kyowa Kirin Pharmaceutical Development, Inc. submitted a Biologic Licensing Application (BLA 761051) for Poteligeo with the proposed indication of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy.^a The risks associated with mogamulizumab include dermatologic toxicity, infusion-related reactions, infections, autoimmune complications, and increased complications in patients receiving allogeneic hematopoietic stem cell transplantation. The applicant did not submit a proposed REMS or risk management plan with this application.

Should Poteligeo (mogamulizumab) be approved, DRISK has concluded that a REMS is not needed to ensure its benefits outweigh its risks. The likely prescribers are medical oncologists and the adverse events observed in clinical testing are have likewise been observed with other medications used in oncology practice, except perhaps increased complications in patients receiving allogeneic hematopoietic stem cell transplantation. Patients receiving allogeneic hematopoietic stem cell transplantation are under the care of multidisciplinary medical teams who will be able to manage this event.

DRISK and DHP agree that the safety profile for Poteligeo is acceptable for the patient population and healthcare providers who will prescribe and administer Poteligeo are likely to be able to manage the Poteligeo-emergent adverse events without additional risk mitigation measures beyond labeling.

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) Poteligeo (mogamulizumab) is necessary to ensure the benefits outweigh its risks. Kyowa Kirin Pharmaceutical Development, Inc. submitted a Biologic Licensing Application (BLA) 761051 for mogamulizumab with the proposed indication cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy. This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

^a Division of Hematology Products has proposed the indication “the treatment of adult patients with relapsed or refractory mycoses fungoides (MF) or Sezary syndrome (SS) after at least one prior systemic therapy”

Mogamulizumab, a new molecular entity^b, is a recombinant humanized monoclonal antibody that targets CC chemokine receptor 4 (CCR4)-expressing cells. Mogamulizumab is proposed for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

Mogamulizumab will be supplied as a colorless solution injection for intravenous use, 20 mg/5 mL in (b) (4) single-dose vials. The solution is diluted in 0.9% saline solution, to a final concentration 0.1 to 3 mg/mL and then infused over one hour, in a healthcare setting capable of administering intravenous infusions. Mogamulizumab is to be dosed on days 1, 8, 15, and 22 of the first 28-day cycle, and then on days 1 and 15 of subsequent cycles until disease progression or unacceptable toxicity.^c

Mogamulizumab was granted orphan drug designation (November 2, 2010), and breakthrough designation (August 22, 2017) for the treatment of mycoses fungoides and Sezary syndrome, two of the most common forms of CTCL. Mogamulizumab is approved in Japan, having received approval in 2012 for CTCL, and receiving subsequent approval in 2014 for adult T-cell leukemia-lymphoma.

The efficacy of mogamulizumab is being studied in a number of cancers and in Human T cell lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP).¹

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761051 relevant to this review:

- 11/02/2010: Orphan designation granted
- 08/22/17: Breakthrough designation granted for the treatment of mycoses fungoides and Sezary syndrome
- 03/09/2016: Pre-BLA meeting held; REMS not discussed
- 10/04/2017: BLA 761051 submission for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy received
- 11/22/2017: Priority review granted; PDUFA 6/4/18; Applicant notified that unspecified earlier action possible (internal goal action date 3/23/18)
- 01/17/2018: 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 Poteligeo; the Agency informed the Applicant that the indication would be limited to mycoses fungoides and Sezary syndrome

3 Therapeutic Context and Treatment Options

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

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

3.1 DESCRIPTION OF THE MEDICAL CONDITION

T-cell lymphoma is a form of non-Hodgkin's lymphoma. One of the most common forms of T-cell lymphoma is CTCL, T-cell lymphomas that involve the skin. Cutaneous T-cell lymphoma is rare, but potentially life-threatening. CTCL affects men more often than women, and usually occurs in men in their sixth and seventh decades of life. Some patients with early-stage CTCL never progress to later stages, while other patients progress rapidly, with the cancer spreading to lymph nodes and internal organs. Mycoses fungoides, the most common type of CTCL, occurs in 16,000 to 20,000 patients in the United States.^d Sezary syndrome is an advanced, variant form of mycoses fungoides.²

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The following table, prepared by the Clinical Reviewer, summarizes the available therapies for CTCL.³

Available therapies for CTCL

Drug	Class	Indication	Pivotal Trial Design	Efficacy *
Brentuximab vedotin (2017)	CD30 antibody-drug conjugate	Adults with pcALCL or CD30-expressing MF after prior systemic therapy	Randomized p 3 (N=131): BV vs. physician choice of MTX or bexarotene	BV vs control: ORR4 56% vs. 12%; CR 16% vs. 2%; HR for PFS 0.27 (95% CI, 0.17 - 0.43)
Romidepsin (2009)	HDAC inhibitor	CTCL after ≥ 1 systemic therapy	Two single-arm studies (N=167)	ORR 34 - 35%
Vorinostat (2006)	HDAC inhibitor	Cutaneous manifestations of CTCL after 2 systemic therapies	Two single-arm studies (N=107)	ORR 30% (all stages and ≥ IIB); Median TTR 2 - 2.7mo
Bexarotene (1999)	Retinoid	Cutaneous manifestations of CTCL in pts refractory to ≥ 1 systemic therapy	Two single-arm, historically controlled studies (N=152) One postmarketing study (N=59)	ORR 30% to 38%
Methotrexate (1959)	Antimetabolite	Alone or in combination with other anticancer agents for advanced MF (CTCL)	Not in PI	ORR up to 50% as single agent

pcALCL = primary cutaneous anaplastic large cell lymphoma
ORR4 = ORR lasting 4 months

* ORR based on skin compartment

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Other therapies, not FDA-approved, include bortezomib (Velcade), denileukin diftitox (Ontak), pralatrexate (Folotyn). Options for refractory disease include alemtuzumab (Campath), liposomal doxorubicin (Doxil), and gemcitabine (Gemzar).⁴

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

4 Benefit Assessment⁵

In a randomized, open-label, multicenter trial⁶ the efficacy of mogamulizumab was examined in patients with mycoses fungoides (MF) or Sezary Syndrome (SS) after at least one prior systemic therapy. The trial randomized 372 patients to either mogamulizumab (186 patients; 56% with MF, 44% with SS) or vorinostat (186 patients; 53% with MF, 44% with SS). The median age of patients was 64 years (range, 25 to 101); 58% were male, and 70% were white.

Mogamulizumab 1 mg/kg was administered intravenously over at least 60 minutes on days 1, 8, 15 and 22 of the first 28-day cycle and on days 1 and 15 of subsequent cycles. Vorinostat was dosed at 400 mg orally once daily, continuously for 28-day cycles. Treatment continued until disease progression or unacceptable toxicity.

The primary efficacy measure was investigator-assessed progression-free survival (PFS). Mogamulizumab significantly prolonged PFS compared to vorinostat. The estimated median PFS was 7.7 months (range, 5.7 to 10.3) for mogamulizumab vs. 3.1 months (range, 2.9 to 5.1) for vorinostat.^e The number with progressive disease was 104 patients in the mogamulizumab group and 128 in the vorinostat group.

5 Risk Assessment & Safe-Use Conditions^{7, f}

The primary efficacy trial also generated the data used to compile the safety database. In addition to the 186 patients randomized to receive mogamulizumab, 135 patients who were randomized to receive vorinostat subsequently were crossed over to receive mogamulizumab; therefore, a total of 319 patients ultimately received mogamulizumab. The duration of exposure to mogamulizumab was 5.6 months (range, less than 1 month to 45 months).

Fatal adverse reactions within 90 days of the last dose occurred in 2.2% (7/319) of patients who received mogamulizumab treatment (randomized or crossover). The reason for the deaths were infection (2), polymyositis and secondary pneumonia (1), acute hypoxia and arrhythmia (1), hypoalbuminemia, anorexia, and general decline (1), GI hemorrhage (1), and pulmonary embolism (1).

Serious adverse reactions were reported in 36% (66/184) of patients randomized to mogamulizumab, most commonly were infection (16% of patients; 30/184). Serious adverse reactions reported in more than 2% of patients in the mogamulizumab group were the following:

- Pneumonia (5%)
- Sepsis (4%)
- Pyrexia (4%)

^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.*

^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.*

- Skin infections (3%)

Other serious adverse reactions, each reported in 2% of patients, included hepatitis, pneumonitis, rash, infusion-related reactions, lower respiratory tract infections, renal insufficiency, and hypercalcemia. Mogamulizumab was discontinued for adverse reactions in 18% of randomized patients, most frequently due to rash or drug eruption (7.1%).

The most important serious adverse reactions are dermatologic toxicity, infusion-related reactions, infections, auto-immune complications, and complications of allogeneic hematopoietic stem cell transplantation (HSCT) post-mogamulizumab.

5.1 DERMATOLOGIC TOXICITY

Section 5.1 of the draft labeling describes the risk of dermatologic toxicity. Of 528 patients treated with mogamulizumab in clinical (b) (4), grade 3 skin adverse reactions were reported in 3.6% (b) (4), grade 4 skin adverse reactions in less than 1% of patients, and Stevens–Johnson syndrome (SJS) in less than 1% of patients. (b) (4)

The draft labeling advises healthcare providers to monitor for rash, and to manage rash with topical steroids and temporary or permanent interruption of therapy with mogamulizumab.

5.2 INFUSION-RELATED REACTIONS

Section 5.2 of the draft labeling describes the risk of infusion-related reactions. Severe (Grade 3) infusion-related reactions occurred in 8% of patients treated with mogamulizumab. Most reactions occurred during or shortly after the first infusion, but infusion reactions occurred with subsequent infusions as well.

The draft labeling advises healthcare providers to consider pre-medication with antihistamines and acetaminophen prior to the first infusion, although there are no data establishing the efficacy of this approach. The draft labeling also advises to monitor for signs and symptoms of infusion-related reactions, and interrupt the infusion for any such reaction.

5.3 INFECTIONS

Section 5.3 of the draft labeling describes the risk of infections (b) (4) of patients randomized to (b) (4) mogamulizumab had Grade 3 or higher infection or an infection-related serious adverse reaction.

The draft labeling advises healthcare providers to monitor for infection, and to treat infections promptly.

5.4 AUTO-IMMUNE COMPLICATIONS

Section 5.4 of the draft labeling describes the risk of auto-immune complications in patients receiving mogamulizumab. Grade 3 or higher immune-mediated (or possibly immune-mediated reactions) included myositis, myocarditis, polymyositis, hepatitis, pneumonitis, and Guillain-Barré syndrome. (b) (4)

The draft labeling advises healthcare providers to interrupt or permanently discontinue therapy for suspected auto-immune complications.

5.5 COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) POST- MOGAMULIZUMAB

Section 5.5 of the draft labeling describes the risk of transplant complications in patients receiving mogamulizumab. Increased risks of transplant complications have been reported in patients who receive allogeneic HSCT after mogamulizumab including severe (grade 3 or 4) acute graft versus host disease (GVHD), steroid-refractory GVHD, and transplant-related death. (b) (4)

The draft labeling advises healthcare providers to follow patients closely for early evidence of transplant-related complications.

6 Expected Postmarket Use

Mogamulizumab is likely to be used in healthcare settings capable of performing laboratory testing and administering intravenous infusions. Likely settings of use include hospitals, outpatient clinics, and oncology medical practices. The adverse events that presented in clinical testing with mogamulizumab would not preclude the use of the mogamulizumab in these settings. Health care personnel within these settings should have the knowledge and training to manage the adverse events that presented in clinical testing.

The patient population likely to receive mogamulizumab will be older patients (median age in clinical testing was 64 years, range, 25 to 101 years) who have received previous treatment for MF or SS. Patients would be expected to be able to report their treatment-emergent signs and symptoms to their health care providers, and to undergo appropriate laboratory testing.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for mogamulizumab beyond routine pharmacovigilance and labeling. The applicant does not propose a Boxed Warning in the labeling. They do propose a patient information document.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of mogamulizumab based on the efficacy and safety information currently available.

The risks associated with mogamulizumab include dermatologic toxicity, infusion-related reactions, infections, auto-immune complications, and complications of allogeneic HSCT post-mogamulizumab, and auto-immune complications. DRISK recommends that, should mogamulizumab be approved, a REMS is not needed to ensure its benefits outweigh its risks. The adverse events observed in clinical testing are known in oncology medical practice except perhaps increased complications in patients receiving allogeneic hematopoietic stem cell transplantation. Patients receiving allogeneic hematopoietic stem cell transplantation are under the care of multidisciplinary medical teams who will be able to manage this event. Patients who receive HSCT will be under the care of HSCT treatment teams experienced with the complications of HSCT. The recommended monitoring and safe-use practices are part of routine oncology practice. Healthcare providers who will prescribe and administer mogamulizumab are likely to be able to manage the mogamulizumab -emergent adverse events with the use of appropriate labeling, and without additional risk mitigation measures. The clinical reviewer agrees with the applicant that none of the adverse reactions warrant a boxed warning in the labeling.

Because the safety database comprises 319 patients with short (median 5.6 months) exposure, it is possible other safety signals will emerge.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. Medical oncologists are the likely healthcare providers who will prescribe and administer mogamulizumab and should be able to manage the mogamulizumab -emergent adverse events without risk mitigation measures, beyond labeling. 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 <https://clinicaltrials.gov>. Accessed January 22, 2018.

² <http://www.lymphoma.org/site/pp.asp?c=bkLTkaOQLmK8E&b=6300151>. Accessed January 19, 2018.

³ Kasamon, Yvette. Clinical presentation of BLA 761051 at mid-cycle meeting. January 16, 2018.

⁴ <http://www.lymphoma.org/site/pp.asp?c=bkLTkaOQLmK8E&b=6300151>. Accessed January 19, 2018.

⁵ Kasamon Y. Efficacy data summarized from Clinical Reviewer's handout at the Mid-cycle Team Review Meeting, January 4, 2018, and from the FDA-edited labeling as of January 22, 2018.

⁶ **Mogamulizumab anti-CCR4 Antibody Versus ComparatOR In CTCL (MAVORIC)**; clinicaltrials.gov, identifier NCT01728805

⁷ Kasamon Y. Safety data summarized from Clinical Reviewer's handout at the Mid-cycle Team Review Meeting, January 4, 2018, and from the FDA-edited labeling as of January 22, 2018.

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/s/

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