PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr POTELIGEO®

Mogamulizumab for injection

20 mg/5 mL single-use vial

Intravenous Infusion, 4 mg/mL

Antineoplastic

ATC Code: L01FX09

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RECENT MAJOR LABEL CHANGES

N/A	

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4

1.1 Pediatrics 4

1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

4 DOSAGE AND ADMINISTRATION 4

4.1 Dosing Considerations 4

4.2 Recommended Dose and Dosage Adjustment 4

4.3 Reconstitution 5

4.4 Administration 6

4.5 Missed Dose 6

5 OVERDOSAGE 6

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 6

7 WARNINGS AND PRECAUTIONS 7

7.1 Special Populations 8

7.1.1 Pregnant Women 8

7.1.2 Breast-feeding 9

7.1.3 Pediatrics 9

7.1.4 Geriatrics 9

8 ADVERSE REACTIONS 10

8.1 Adverse Reaction Overview 10

8.2 Clinical Trial Adverse Reactions 10

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data 13

8.5 Post-Market Adverse Reactions 13
9 DRUG INTERACTIONS 14
9.2 Drug Interactions Overview 14
10 CLINICAL PHARMACOLOGY 14
10.1 Mechanism of Action 14
10.2 Pharmacodynamics 14
10.3 Pharmacokinetics 14
11 STORAGE, STABILITY AND DISPOSAL 15
12 SPECIAL HANDLING INSTRUCTIONS 15
PART II: SCIENTIFIC INFORMATION 15
13 PHARMACEUTICAL INFORMATION 15
14 CLINICAL TRIALS 16
14.1 Trial Design and Study Demographics 16
14.2 Study Results 17
14.4 Immunogenicity 19
15 MICROBIOLOGY 19
16 NON-CLINICAL TOXICOLOGY 19
PATIENT MEDICATION INFORMATION 21

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

POTELIGEO (mogamulizumab for injection) is indicated for:

- the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The safety profile in elderly patients (≥ 65 years) was generally consistent with that of adult patients aged less than 65 years.

2 CONTRAINDICATIONS

- POTELIGEO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- It is recommended that treatment be continued until disease progression or unacceptable toxicity.
- Do not administer POTELIGEO subcutaneously or by rapid intravenous administration.
- It is recommended that premedication with diphenhydramine and acetaminophen be administered for the first POTELIGEO infusion and subsequent infusions, if an infusion reaction occurs.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of POTELIGEO is 1 mg/kg administered as an intravenous infusion over at least 60 minutes. Administer on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle.

Health Canada has not authorized an indication for pediatric use.

Dose Adjustments

Dermatologic Toxicity

Permanently discontinue POTELIGEO for life-threatening (Grade 4) rash or for any Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (see WARNINGS and PRECAUTIONS). If SJS or TEN is suspected, stop POTELIGEO and do not resume unless SJS or TEN has been excluded and the cutaneous reaction has resolved to Grade 1 or less.

If moderate or severe (Grades 2 or 3) rash occurs, interrupt POTELIGEO and treat rash appropriately, including administering at least 2 weeks of topical corticosteroids, until rash improves to Grade 1 or less, at which time POTELIGEO treatment may be resumed (see WARNINGS and PRECAUTIONS).

Infusion Reactions

Permanently discontinue POTELIGEO for a life-threatening (Grade 4) infusion reaction (see WARNINGS and PRECAUTIONS). Temporarily interrupt the infusion of POTELIGEO for mild to severe (Grades 1 to 3) infusion reactions and treat symptoms. Reduce the infusion rate by at least 50% when restarting the infusion after symptoms resolve. If reaction recurs and is unmanageable, discontinue infusion (see WARNINGS and PRECAUTIONS). If an infusion reaction occurs, administer premedication (such as diphenhydramine and acetaminophen) for subsequent POTELIGEO infusions.

4.3 Reconstitution

Parenteral Products:

Reconstitution for Direct Intravenous Infusion

Vial Size	Volume of Diluent to be Added to Intravenous Bag	Approximate Available Volume	Concentration per mL
20 mg / 5 mL	0.9% Sodium Chloride Injection, USP	The dose (mg/kg) and number of vials needed is calculated based on patient weight	The final concentration of diluted solution should be between 0.1 mg/mL to 3.0 mg/mL

Visually inspect drug product solution for particulate matter and discoloration prior to administration. POTELIGEO is a clear to slightly opalescent colorless solution. Discard the vial if cloudiness, discoloration, or particulates are observed.

Calculate the dose (mg/kg) and number of vials of POTELIGEO needed to prepare the infusion solution based on patient weight.

Aseptically withdraw the required volume of POTELIGEO into the syringe and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL.

Mix diluted solution by gentle inversion. Do not shake.

Discard any unused portion left in the vial.

The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

After preparation, infuse the POTELIGEO solution immediately, or store under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation.

Do not freeze. Do not shake.

4.4 Administration

Administer infusion solution over at least 60 minutes through an intravenous line containing a sterile, low protein binding, 0.22 micron (or equivalent) in-line filter.

Do not mix POTELIGEO with other drugs.

Do not co-administer other drugs through the same intravenous line.

4.5 Missed Dose

Administer POTELIGEO within 2 days of the scheduled dose.

If a dose is missed, administer the next dose as soon as possible and resume dosing schedule.

5 OVERDOSAGE

The maximum tolerated dose of POTELIGEO has not been determined. In case of overdosage, patients should be closely monitored for signs and symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted.

For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous Infusion	Solution for infusion 4mg/ml	Citric acid monohydrate, glycine, polysorbate 80, water for injection (USP) May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5

Description

POTELIGEO (mogamulizumab for injection) is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody targeting CC chemokine receptor 4 (CCR4)-expressing cells. Mogamulizumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies.

7 WARNINGS AND PRECAUTIONS

Autoimmune Complications

Fatal and life-threatening immune-mediated complications have been reported in recipients of POTELIGEO. In Study 0761-010, Grade 3 or higher immune-mediated or possibly immune-mediated reactions have been observed during use of POTELIGEO, including myositis (<1%), myocarditis (<1%), hepatitis (<1%), pneumonitis (<1%), and a variant of Guillain-Barré syndrome (<1%). Polymyositis was reported in one patient (<1%) with a fatal outcome.

Interrupt or permanently discontinue POTELIGEO as appropriate for suspected immune-mediated adverse reactions. Consider the benefit/risk of POTELIGEO in patients with a history of autoimmune disease.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients Treated with POTELIGEO

Complications, including severe (Grade 3 or 4) acute graft versus host disease (GVHD), steroid-refractory GVHD, and transplant-related death have been reported in patients who received allogeneic HSCT after POTELIGEO.

A higher risk of transplant complications has been reported when POTELIGEO was last administered within 50 days prior to HSCT as compared to last administration greater than 50 days prior to HSCT. The role of POTELIGEO in patients who developed GVHD after HSCT has not been established. If HSCT is considered clinically appropriate, follow patients closely for early evidence of transplant-related complications.

The safety of treatment with POTELIGEO after autologous or allogeneic HSCT has not been studied.

Dermatologic Toxicity

Serious skin reactions, including SJS and TEN, have been reported in patients treated with POTELIGEO; some of these cases were life-threatening and some with fatal outcomes.

Rash (drug eruption) is one of the most common adverse reactions associated with POTELIGEO and the most frequent adverse drug reaction leading to discontinuation (7.1% or 13/184). In Study 0761-010, the incidence of treatment-related drug eruption was 23.9%. The majority of drug eruption was Grade 1 (8.2%) or Grade 2 (10.9%); 4.9% of subjects had Grade 3 drug eruption, and no subject had a Grade 4 or 5 drug eruption.

The onset of drug eruption is variable. The affected areas and appearance are also variable.

Patients should be closely monitored for skin reaction throughout the treatment course.

Consider skin biopsy to help distinguish drug eruption from disease progression.

Discontinue POTELIGEO permanently for SJS or TEN or any life-threatening (Grade 4) reaction. For possible SJS or TEN, interrupt POTELIGEO and do not restart unless SJS or TEN is ruled out and the cutaneous reaction has resolved to Grade 1 or less.

Infections

Fatal and serious infections have been reported in patients treated with POTELIGEO. The most frequently reported treatment-related serious infections in Study 0761-010 were pneumonia (2.2%), cellulitis (1.6%) and sepsis (1.1%). Monitor patients for signs and symptoms of infection and treat promptly.

Infusion-Related Reactions

Fatal and life-threatening infusion-related reactions (IRRs) have been reported in patients treated with POTELIGEO. In Study 0761-010, IRRs were mostly mild or moderate in severity (incidence of Grade 1 was 16.3% and Grade 2 was 15.2%), although severe IRRs have occurred (Grade 3 in 1.6% of subjects). No Grade 4 or 5 IRRs were reported. The majority of IRRs occur during or shortly after the first infusion. IRRs can also occur with subsequent infusions. The most commonly reported signs include chills, nausea, fever, tachycardia, rigors, headache and vomiting.

Consider premedication (such as diphenhydramine and acetaminophen) for the first infusion of POTELIGEO and subsequent infusions, if an infusion reaction occurs.

Patients should be carefully monitored for signs and symptoms of infusion reactions during and after infusion. If an IRR occurs, the infusion should be interrupted, and appropriate medical management instituted immediately.

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on POTELIGEO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of POTELIGEO to pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for adverse developmental outcomes at maternal systemic exposures 27 times the exposure in patients at the recommended dose, based on AUC (see Data).

In general, IgG molecules are known to cross the placental barrier and in the monkey reproduction study mogamulizumab was detected in fetal plasma. Therefore, POTELIGEO has the potential to be transmitted from the mother to the developing fetus.

POTELIGEO is not recommended during pregnancy or in women of childbearing potential not using contraception.

If POTELIGEO use is necessary in women of childbearing potential, advise using effective contraception during POTELIGEO treatment and for at least 6 months after the last dose of POTELIGEO.

Animal Data

The effects of mogamulizumab on embryo-fetal development were evaluated in 12 pregnant cynomolgus monkeys that received mogamulizumab once weekly by intravenous administration from the start of organogenesis through delivery at an exposure level 27 times higher than the clinical dose. Mogamulizumab administration did not show a potential for embryo-fetal lethality, teratogenicity, or fetal growth retardation and did not result in spontaneous abortion or increased fetal death. In surviving fetuses (10 of 12 compared with 11 of 12 in the control group) of cynomolgus monkeys treated with mogamulizumab, a decrease in CCR4-expressing lymphocytes due to the pharmacological activity of mogamulizumab was noted; there were no apparent mogamulizumab-related external, visceral, or skeletal abnormalities.

7.1.2 Breast-feeding

It is unknown if POTELIGEO is excreted in human milk, the potential effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for POTELIGEO and any potential adverse effects on the breastfed child from POTELIGEO or from the underlying maternal condition.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Among 184 subjects randomized to receive POTELIGEO in the randomized period of Study 0761-010, 85 (46.2%) were ≥65 years. No overall differences in effectiveness were observed between these patients and younger patients. The overall incidence of TEAEs was similar for subjects <65 years of age (96.0%, 95/99) and those ≥65 years (98.8%, 84/85).

Differences (approximately 10% or greater) between age groups in incidences of TEAEs by SOC and/or individual preferred terms were as follows:

- Infections and Infestations (<65 years, 68.7%; ≥65 years, 58.8%);
- Folliculitis (<65 years, 12.1%; ≥65 years, 1.2%);
- Skin infection (<65 years, 14.1%; ≥65 years, 3.5%);
- Drug eruption (<65 years, 18.2%; ≥65 years, 30.6%);
- Headache (<65 years, 18.2%; ≥65 years, 5.9%);
- Hypokalaemia (<65 years, 1.0%; ≥65 years, 10.6%);
- Neoplasms, Benign, Malignant and Unspecified (<65 years, 8.1%; ≥65 years, 18.8%)

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Serious adverse reactions

- Autoimmune Complications *[see Warnings and Precautions]*
- Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in Patients Treated with POTELIGEO *[see Warnings and Precautions]*
- Dermatologic Toxicity *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Infusion-Related Reactions *[see Warnings and Precautions]*

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse Reactions

The data described below reflect exposure to POTELIGEO in a randomized, open-label, actively controlled clinical trial (Study 0761-010) for adult patients with MF or SS who received at least one prior systemic therapy. Of 370 patients treated, 184 (57% with MF, 43% with SS) received POTELIGEO as randomized treatment and 186 (53% with MF, 47% with SS) received vorinostat. 135 (73%) patients randomized to receive vorinostat crossed over to POTELIGEO. A total of 319 patients received POTELIGEO.

POTELIGEO was administered at 1 mg/kg 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 28-day cycles. Premedication (diphenhydramine, acetaminophen) was optional and administered to 65% of randomized patients for the first infusion. The comparator group received vorinostat 400 mg orally once daily, given continuously in 28-day cycles. Treatment continued until unacceptable toxicity or progressive disease.

The median age was 64 years (range, 25 to 101 years), 58% of patients were male, 70% were white, and 99% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients had a median of 3 prior systemic therapies. The trial required an absolute neutrophil count (ANC) ≥1,500/µL (≥1,000/µL if bone marrow was involved), platelet count ≥100,000/µL (≥75,000/µL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine ≤1.5 mg/dL, and hepatic transaminases ≤2.5 times upper limit of normal (ULN) (≤5 times ULN if lymphomatous liver infiltration). Patients with active autoimmune disease, active infection, autologous HSCT within 90 days, or prior allogeneic HSCT were excluded.

During randomized treatment, the median duration of exposure to POTELIGEO was 5.6 months, with 48% (89/184) of patients with at least 6 months of exposure and 23% (43/184) with at

least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months, with 22% (41/186) of patients with at least 6 months of exposure.

Serious adverse reactions for POTELIGEO observed in the study included infections (pneumonia 2.2%, cellulitis 1.6%, sepsis 1.1%), pyrexia (2.2%), and infusion-related reaction (1.6%).

The most frequent adverse drug reaction leading to discontinuation among POTELIGEO treated patients was drug eruption 7.1% (13/184).

Table 1 summarizes common adverse reactions having a ≥2% higher incidence with POTELIGEO than with vorinostat in Study 0761-010.

Table 1 Common Adverse Reactions (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Adverse Reactions by Body System [a, b, c]	Vorinostat (N=186)		POTELIGEO (N=184)		Crossover to POTELIGEO (N=135)	
	All Grades n (%)	≥Grade 3 n (%)	All Grades n (%)	≥Grade 3 n (%)	All Grades n (%)	≥Grade 3 n (%)
Skin and Subcutaneous Tissue Disorders						
Rash, Including Drug Eruption	22 (12)	2 (1)	67 (36)	7 (4)	54 (40)	5 (4)
Drug Eruption	2 (1)	0	46 (25)	9 (5)	37 (27)	4 (3)
Procedural Complications						
Infusion Related Reaction	1 (<1)	0	61 (33)	3 (2)	51 (38)	6 (4)
Infections						
Upper Respiratory Tract Infection	29 (16)	2 (1)	40 (22)	0	28 (21)	0
Skin Infection	25 (13)	6 (3)	34 (18)	5 (3)	21 (16)	0
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal Pain	32 (17)	3 (2)	40 (22)	1 (<1)	31 (23)	0
General Disorders						
Pyrexia	12 (6)	0	33 (18)	1 (<1)	17 (13)	0
Gastrointestinal						
Mucositis	11 (6)	0	26 (14)	2 (1)	19 (14)	0

[a] Adverse reactions include groupings of individual preferred terms.

[b] Includes adverse reactions reported up to 90 days after randomized treatment.

[c] Includes all common adverse reactions only (≥10%) for the crossover group.

Rash/Drug Eruption includes: dermatitis (allergic, atopic, bullous, contact, exfoliative, infected), drug eruption, palmoplantar keratoderma, rash (generalized, macular, maculopapular, papular, pruritic, pustular), skin reaction, toxic skin eruption

Upper Respiratory Tract Infection includes: laryngitis viral, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

Skin Infection includes: cellulitis, dermatitis infected, erysipelas, impetigo, infected skin ulcer, periorbital cellulitis, skin bacterial infection, skin infection, staphylococcal skin infection

Musculoskeletal Pain includes: back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity

Adverse Reactions by Body System [a, b, c]	Vorinostat (N=186)		POTELIGEO (N=184)		Crossover to POTELIGEO (N=135)	
	All Grades n (%)	≥Grade 3 n (%)	All Grades n (%)	≥Grade 3 n (%)	All Grades n (%)	≥Grade 3 n (%)

Mucositis includes: aphthous stomatitis, mouth ulceration, mucosal inflammation, oral discomfort, oral pain, oropharyngeal pain, stomatitis

Other Common Adverse Reactions in ≥10% of POTELIGEO Arm [a, b]

- **General disorders:** fatigue (31%), edema (17%)
- **Gastrointestinal disorders:** diarrhea (30%), nausea (17%), constipation (13%)
- **Blood and lymphatic system disorders:** thrombocytopenia (14%), anemia (12%)
- **Nervous system disorders:** headache (15%)
- **Vascular disorders:** hypertension (10%)
- **Respiratory disorders:** cough (13%)

Adverse Reactions in ≥5% but <10% of POTELIGEO Arm [a, b]

- **Infections:** urinary tract infection (10%), candidiasis (9%), folliculitis (8%), pneumonia (7%), herpesvirus infection (5%)
- **Investigations:** renal insufficiency (9%), hyperglycemia (9%), weight increase (8%), hypokalemia (7%), weight decrease (6%), hypomagnesemia (6%)
- **Psychiatric disorders:** insomnia (9%), depression (7%)
- **Skin and subcutaneous disorders:** xerosis (9%), alopecia (8%)
- **Nervous system disorders:** dizziness (9%), peripheral neuropathy (7%)
- **Metabolism and nutrition disorders:** decreased appetite (9%)
- **Respiratory disorders:** dyspnea (7%)
- **General disorders:** chills (7%)
- **Gastrointestinal disorders:** vomiting (7%), abdominal pain (7%)
- **Injury, poisoning and procedural complications:** fall (6%)
- **Musculoskeletal disorders:** muscle spasms (5%)
- **Cardiovascular disorders:** arrhythmia (5%)
- **Eye disorders:** conjunctivitis (5%)

Selected Other Adverse Reactions [a, b]

- Tumor lysis syndrome (<1%)
- Myocardial ischemia or infarction (<1%)
- Cardiac failure (<1%)
- Cytomegalovirus infection (<1%)

[a] Includes grouped terms
[b] From 184 patients randomized to POTELIGEO

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 2 summarizes common treatment-emergent laboratory abnormalities having a ≥2% higher incidence with POTELIGEO than with vorinostat in Study 0761-010.

Table 2: Common New or Worsening Laboratory Abnormalities (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Laboratory Test [a,b]	Vorinostat (N=186)		POTELIGEO (N=184)		Crossover to POTELIGEO (N=135)	
	All Grades n (%)	≥Grade 3 n (%)	All Grades n (%)	≥Grade 3 n (%)	All Grades n (%)	≥Grade 3 n (%)
Chemistry						
Albumin Decreased	50 (27)	5 (3)	67 (36)	6 (3)	32 (24)	2 (2)
Calcium Decreased	39 (21)	4 (2)	56 (30)	5 (3)	40 (30)	0
Uric Acid Increased	20 (11)	20 (11)	57 (31)	57 (31)	40 (30)	40 (30)
Phosphate Decreased	49 (26)	10 (5)	51 (28)	10 (5)	36 (27)	5 (4)
Magnesium Decreased	15 (8)	1 (<1)	34 (19)	1 (<1)	28 (21)	2 (2)
Glucose Decreased	15 (8)	1 (<1)	27 (15)	1 (<1)	24 (18)	0
Calcium Increased	15 (8)	1 (<1)	22 (12)	1 (<1)	16 (12)	0
Hematology						
CD4 Lymphocytes Decreased [c]	8 (4)	3 (2)	73 (40)	45 (25)	45 (33)	25 (19)
Lymphocytes Decreased	56 (30)	21 (11)	140 (76)	85 (46)	111 (82)	68 (50)
White Blood Cells Decreased	33 (18)	3 (2)	60 (33)	3 (2)	54 (40)	2 (2)

[a] Includes laboratory abnormalities, reported up to 90 days after treatment, that are new or worsening in grade or with worsening from baseline unknown.

[b] Includes all common new or worsening laboratory abnormalities only (≥10%) for the crossover group.

[c] Out of 99 evaluable recipients of POTELIGEO and 36 evaluable recipients of vorinostat.

Other common treatment-emergent laboratory abnormalities in the POTELIGEO arm included hyperglycemia (54%; 5% Grade 3-4), anemia (35%; 3% Grade 3-4), thrombocytopenia (29%, 0% Grade 3-4), aspartate transaminase (AST) increased (26%; 2% Grade 3-4), alanine transaminase (ALT) increased (19%; 2% Grade 3-4), alkaline phosphatase increased (17%; 0% Grade 3-4), and neutropenia (11%; 2% Grade 3-4).

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of POTELIGEO.

- Infections: Hepatitis B virus reactivation
- Cardiac disorders: Stress cardiomyopathy

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been conducted with POTELIGEO.

Mogamulizumab is primarily metabolized through catabolic pathways. Therefore, it is not expected that POTELIGEO will have drug-drug interactions with other medicinal products.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Mogamulizumab is a defucosylated, humanized IgG1 kappa monoclonal antibody that binds to CCR4, a G protein-coupled receptor for CC chemokines that is involved in the trafficking of lymphocytes to various organs. Non-clinical in vitro studies demonstrate mogamulizumab binding targets a cell for antibody-dependent cellular cytotoxicity (ADCC) resulting in depletion of the target cells. CCR4 is expressed on the surface of some T-cell malignancies and is expressed on regulatory T-cells (Treg) and a subset of Th2 T-cells.

10.2 Pharmacodynamics

Mogamulizumab exposure-response relationships and the time course of pharmacodynamics response are unknown.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of mogamulizumab was evaluated in adult patients with T-cell malignancies over a dose range of 0.01 to 1 mg/kg (0.01 to 1 times the approved recommended dosage). Based on the population PK analysis, the exposure of mogamulizumab increased proportionally with dose.

Following repeated dosing of the approved recommended dosage, steady state concentrations were reached after 8 doses (12 weeks), and the systemic accumulation was 1.6 fold. At steady state, the peak concentration (Cmax,ss) is 32 (68%) µg/mL, the trough concentration (Cmin,ss) is 11 (239%) µg/mL, and AUCss is 5,577 (125%) µg•h/mL.

Distribution:

The geometric mean (% geometric coefficient of variation [GCV%]) central volume of distribution (Vc) was 3.57 L (20.1%).

Elimination

The geometric mean (GCV%) clearance (CL) is 12.0 mL/h (83.7%) and elimination half-life (t1/2) is 17 days (65.5%).

Special Populations and Conditions

No clinically significant changes in the PK of mogamulizumab were observed based on age (range: 22 to 101 years), sex, ethnicity, renal impairment (creatinine clearance <90 mL/min, estimated by Cockcroft-Gault), mild (total bilirubin ≤ ULN and AST <ULN, or total bilirubin <1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment, disease subtype (MF or SS), degree of CCR4 expression, or ECOG status. The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST) on mogamulizumab PK is unknown.

11 STORAGE, STABILITY AND DISPOSAL

POTELIGEO vials must be stored in the original carton until the time of use under refrigerated conditions at 2°C to 8°C. Keep POTELIGEO vial in the original carton to protect from light until time of use.

Do not freeze or shake POTELIGEO.

Do not use POTELIGEO beyond the expiration date stamped on the carton/vial.

POTELIGEO vials are single-use only. Discard any unused product.

After opening: POTELIGEO does not contain a preservative. Once opened, the medicinal product should be diluted and infused immediately.

After preparation of infusion: If the product is not infused immediately, in use storage times and conditions prior to use must not be longer than a total of 24 hours at 2°C – 8°C provided that dilution has taken place under controlled and validated aseptic conditions.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: mogamulizumab

Chemical name: IgG1 immunoglobulin, anti CC chemokine receptor 4 (CCR4), recombinant humanized monoclonal antibody.

Molecular mass: the observed molecular weight of the most abundant form of the intact antibody is 149 kDa.

Structural formula: mogamulizumab is an IgG1 monoclonal antibody subtype and contains 32 cysteine residues. A correctly folded antibody molecule includes 4 disulfide linkages as interchain bonds and 12 intrachain bonds.

Physicochemical properties: aqueous solution stored frozen at -70°C at a concentration of 8.5-10.5 mg/mL in 5 mM sodium citrate buffer, pH 4.7-5.3.

The mogamulizumab drug substance solution is clear to slightly opalescent, colorless solution. The solution is practically free from particles.

The pH of mogamulizumab drug substance is 4.7-5.3.

The theoretical extinction coefficient of mogamulizumab at 280 nm is 1.4 L·g-1·cm-1.

The isoelectric point of mogamulizumab is 8.1-8.7.

Pharmaceutical standard: mogamulizumab drug substance reference standard has been developed and appropriately characterized in-house at the drug substance manufacturing site.

Product Characteristics:

POTELIGEO is a sterile, preservative-free, clear to slightly opalescent colorless solution provided in a single-use vial for dilution prior to intravenous infusion. Each vial contains 20 mg of mogamulizumab in 5 mL of solution. Vials are individually packaged in a carton.

Prior to IV administration, POTELIGEO is withdrawn into a syringe and transferred into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL. The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 Summary of patient demographics for clinical trials in MF or SS

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
0761-010	Randomized, open-label, multicenter trial	POTELIGEO: Administered 1 mg/kg intravenously weekly for 4 weeks, then every other week Vorinostat: 400 mg orally once daily	n = 372	63 years (25 to 101)	Male: 216 Female: 156

Study 0761-010

A randomized, open-label, multicenter trial evaluated the efficacy of POTELIGEO in adult patients with MF or SS who received at least one prior systemic therapy. The trial randomized 372 patients 1:1 to either POTELIGEO (186 patients; 56% with MF, 44% with SS) or vorinostat (186 patients; 53% with MF, 47% with SS). The trial included patients regardless of tumor CCR4 expression status and excluded patients with histologic transformation, prior allogeneic HSCT, autologous HSCT within 90 days, active autoimmune disease, or active infection. The trial required patients to have ANC ≥1,500/µL (≥1,000/µL if bone marrow was involved), platelet count ≥100,000/µL (≥75,000/µL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine ≤1.5 mg/dL and hepatic transaminases ≤2.5 times ULN (≤5 times ULN if lymphomatous liver infiltration).

The dose of POTELIGEO was 1 mg/kg 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 each subsequent cycle. Vorinostat was dosed at 400 mg orally once daily, continuously for 28-day cycles. Treatment continued until disease progression or unacceptable toxicity. Vorinostat-treated patients with disease progression or unacceptable toxicities were permitted to cross over to POTELIGEO.

The median age was 64 years (range: 25 to 101), 58% of patients were male, and 70% were white. At study baseline, 38% had stage IB-II disease, 10% stage III, and 52% stage IV. The median number of prior systemic therapies was 3. In the POTELIGEO arm, baseline CCR4 expression status by immunohistochemistry was available in 140 patients (75%), of whom all had CCR4 detected on ≥1% of lymphocytes on skin biopsy, and 134/140 (96%) had CCR4 detected on ≥10% of the lymphocytes. CCR4 expression status was similar in the vorinostat arm.

During randomized treatment, the median duration of exposure to POTELIGEO was 5.6 months (range: <1 to 45.3 months), with 48% of patients with at least 6 months of exposure and 23% with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months (range: <1 to 34.8 months), with 22% of patients with at least 6 months of exposure.

Efficacy was based on investigator-assessed progression-free survival (PFS), which was defined as the time from the date of randomization until documented progression of disease or death. Other efficacy measures included overall response rate (ORR) based on global composite response criteria that combine measures from each disease compartment (skin, blood, lymph nodes and viscera). Responses required confirmation at two successive disease assessments, which included the modified Severity Weighted Assessment Tool, skin photographs, central flow cytometry, and computed tomography.

14.2 Study Results

The trial demonstrated that POTELIGEO significantly prolonged PFS compared to vorinostat (Table 5). The Kaplan-Meier curve for PFS by Investigator is shown in Figure 1. The estimated median follow-up for investigator-assessed PFS was 13 months in the POTELIGEO arm and 10.4 months in the vorinostat arm. By independent review committee assessment, the estimated

median PFS was 6.7 months (95% CI, 5.6 to 9.4) in the POTELIGEO arm and 3.8 months (95% CI, 3.0 to 4.7) in the vorinostat arm (hazard ratio 0.64; 95% CI: 0.49, 0.84).

Figure 1 Kaplan-Meier Curve for Progression-Free Survival per Investigator

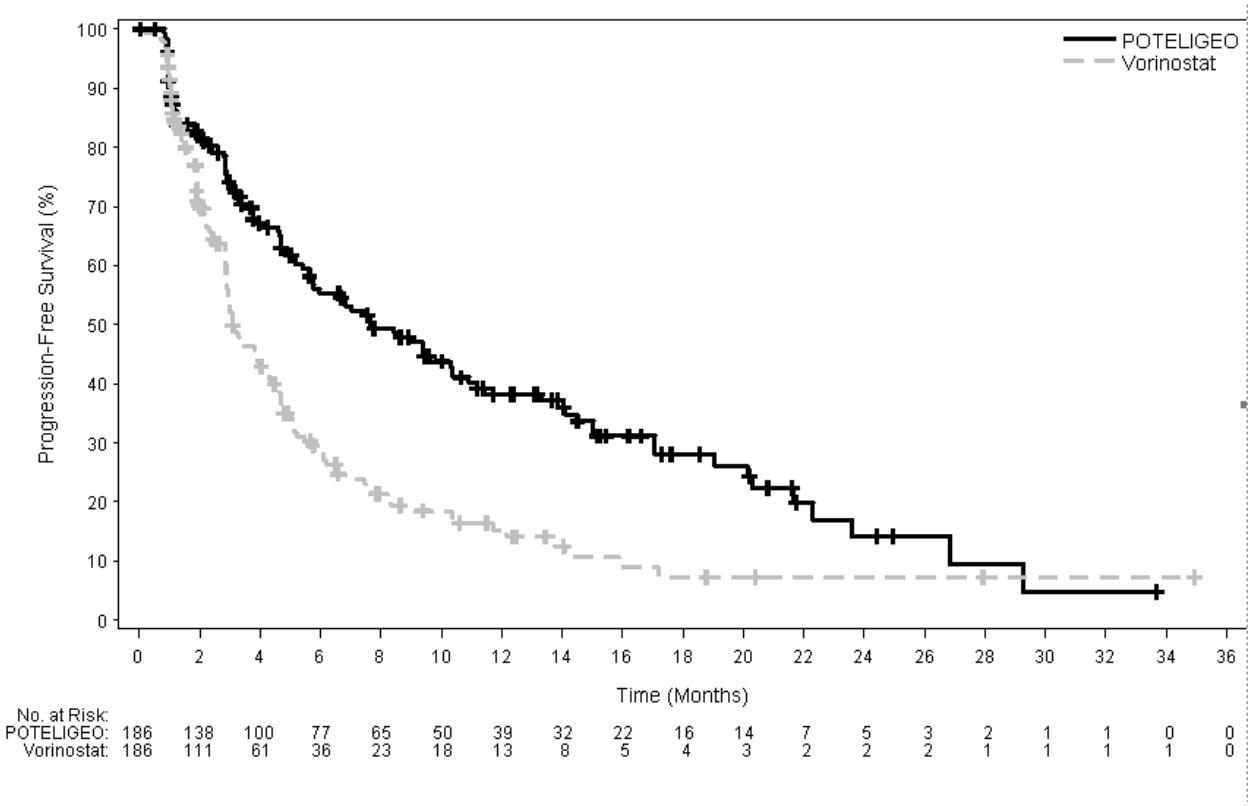

Table 5 Efficacy of Randomized Treatment (Study 0761-010)

Outcome per Investigator	**POTELIGEO N=186**	**Vorinostat N=186**
PFS		
Number of events, n	110	131
Progressive disease	104	128
Death	6	3
Median PFS (95% CI) (months) [a]	7.7 (5.7, 10.3)	3.1 (2.9, 4.1)
Hazard ratio (95% CI) Log rank p-value	0.53 (0.41, 0.69) <.001	
Overall response rate (confirmed CR + PR), n (%) [b, c]	52 (28)	9 (5)
95% CI	(22, 35)	(2, 9)
P-value [d]	<.001	
Duration of overall response (months)		
Median (95% CI) [a]	14.1 (9.4, 19.2)	9.1 (4.7, -)
Confirmed best overall response [b]		
CR, n (%)	5 (3)	0 (0)

95% CI	(1, 6)	(0, 2)
PR, n (%)	47 (25)	9 (5)
95% CI	(20, 33)	(2, 9)
Response by compartment (confirmed CR + PR) [c]		
Blood	n=122	n=123
Response rate, n (%)	83 (68)	23 (19)
95% CI	(59, 76)	(12, 27)
Skin	n=186	n=186
Response rate, n (%)	78 (42)	29 (16)
95% CI	(35, 49)	(11, 22)
Lymph nodes	n=124	n=122
Response rate, n (%)	21 (17)	5 (4)
95% CI	(11, 25)	(1, 9)
Viscera	n=3	n=3
Response rate, n (%)	0 (0)	0 (0)
95% CI	(0, 71)	(0, 71)

[a] Kaplan-Meier estimate.
[b] Based on Global Composite Response score.
[c] Responses in blood and skin must have persisted for at least 4 weeks to be considered confirmed and were evaluated every 4 weeks for the first year. Responses in lymph nodes, visceral disease and overall were evaluated every 8 weeks for the first year.
[d] From Cochran-Mantel-Haenszel test adjusted for disease type, stage, and region.
CI=confidence interval; CR=complete response; NE=not estimable; PR=partial response

14.4 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to POTELIGEO.

Among 263 patients treated with POTELIGEO in Study 0761-010, 37 (14.1%) tested positive for treatment-emergent anti-mogamulizumab antibodies. There were no patients identified to have positive neutralizing antibody responses.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single-dose and repeat-dose studies up to 6 months were conducted in cynomolgus monkeys; there were no mogamulizumab-related toxicities observed in males or females at doses up to 40 mg/kg (60.3- to 94.6-fold higher than the recommended clinical dose).

Anti-mogamulizumab antibodies were detected in some animals receiving a single- or repeat-dose IV injection of mogamulizumab. In animals in which anti-mogamulizumab antibodies were

observed, plasma mogamulizumab concentrations decreased more rapidly than the plasma concentration in animals that did not produce anti-mogamulizumab antibodies. No anti-mogamulizumab antibody-related toxicological findings were noted in the animals in which the production of anti-mogamulizumab antibodies occurred.

Based on observations of skin-related side effects in human patients treated with mogamulizumab, weekly doses of mogamulizumab up to 8 weeks were administered to aged female cynomolgus monkeys as there were no comparable observations in toxicity studies. Although erythema was observed in some of the aged monkeys during mogamulizumab administration, the lesions were mild and transient. There was no clear relationship evident between development of the mild dermatitis and changes in lymphocyte subsets. Thus, the pathogenesis of the human skin disorders associated with mogamulizumab could not be modelled even with aged cynomolgus monkeys.

Carcinogenicity: No specific studies have been conducted to evaluate potential effects on fertility. No carcinogenicity or genotoxicity studies have been conducted with POTELIGEO.

No specific studies have been conducted to evaluate potential effects of POTELIGEO on fertility. No mogamulizumab-related toxic effects in the male and female reproductive organs were observed in sexually mature monkeys in repeat-dose toxicology studies up to 26 weeks in duration.

Reproductive and Developmental Toxicology: In an animal reproductive and developmental toxicity study, administration of mogamulizumab to pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for embryo-fetal lethality, teratogenicity, or fetal growth retardation. In general, IgG molecules are known to cross the placental barrier and mogamulizumab concentrations in fetus plasma were detected. Pharmacological activity of mogamulizumab was noted in fetuses as was evident from a decrease in CCR4 expressing lymphocytes.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

POTELIGEO

Mogamulizumab for Injection

POTELIGEO may cause serious side effects that can be severe, life-threatening or lead to death.

Read this carefully before you start taking **POTELIGEO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **POTELIGEO**.

What is POTELIGEO used for?

- POTELIGEO is a prescription medicine used to treat mycosis fungoides (MF) or Sézary syndrome (SS) in adults when you have tried at least one prior medicine (taken by mouth or injection) and it did not work or the disease has come back.

How does POTELIGEO work?

POTELIGEO is a monoclonal antibody that binds to certain cancerous T-cells, triggering your body's immune cells to specifically target them.

What are the ingredients in POTELIGEO?

Medicinal ingredients: mogamulizumab

Non-medicinal ingredients: citric acid monohydrate, glycine, polysorbate 80, and Water for Injection, USP

POTELIGEO comes in the following dosage forms:

20 mg / 5 mL (4 mg / mL) solution in a single-use vial

Do not use POTELIGEO if:

- You are allergic to POTELIGEO or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take POTELIGEO. Talk about any health conditions or problems you may have, including if you:

- have had a severe skin reaction after receiving POTELIGEO.
- have had an infusion-related reaction during or after receiving POTELIGEO.
- have human immunodeficiency virus (HIV), herpes, cytomegalovirus (CMV), or hepatitis B or C infection, or other on-going infections.
- have a history of autoimmune problems.
- have undergone or plan to have a stem cell transplant, using stem cells from a donor.

- are pregnant or plan to become pregnant. It is not known if POTELIGEO will harm your unborn baby.
    - If you are able to become pregnant, your healthcare provider will do a pregnancy test before you start treatment with POTELIGEO.
    - **Females** who are able to become pregnant should use an effective method of birth control during treatment with POTELIGEO and for at least 6 months after the last dose of POTELIGEO. Talk to your healthcare provider about birth control methods that you can use during this time. Tell your healthcare provider right away if you become pregnant during treatment with POTELIGEO.
- are breastfeeding or plan to breastfeed. It is not known if POTELIGEO passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with POTELIGEO.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Studies to test how POTELIGEO interacts with other medicines have not been done.

How to take POTELIGEO:

- Your healthcare provider will give you POTELIGEO into your vein through an intravenous (IV) line over at least 60 minutes.
- POTELIGEO is usually given on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each 28-day cycle thereafter.
- Your healthcare provider will decide how many treatments you need based on how well you respond and tolerate the treatment.
- If you miss any appointments call your healthcare provider as soon as possible.

Usual dose:

The dose is based on your body weight. Your health care professional will work out the right dose for you.

Overdose:

POTELIGEO is administered under the supervision of a health professional, who will check that the correct dose has been given and treat any overdose.

If you think you, or a person you are caring for, have taken too much POTELIGEO, contact a healthcare professional, hospital emergency department, or regional poison control center immediately, even if there are no symptoms.

Missed Dose:

POTELIGEO should be administered within 2 days of the scheduled dose. If a dose is missed, your healthcare provider should administer the next dose as soon as possible and resume the dosing schedule.

What are possible side effects from using POTELIGEO?

POTELIGEO may cause serious side effects that can be severe, life-threatening or lead to death.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

These are not all the possible side effects you may have when taking POTELIGEO. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of POTELIGEO include:

- Rash
- Tiredness
- Diarrhea
- Constipation
- Nausea
- Stomatitis (mouth ulcer)
- Fever
- Swollen legs or ankles
- Headache
- Infusion reaction

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Skin Problems: • skin pain • itching • skin blistering or peeling • rash • painful sores or ulcers in your mouth, nose, throat, or genital area		√	
Infusion reactions: • chills or shaking • redness on your face (flushing) • itching or rash		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
• shortness of breath, coughing, or wheezing • dizziness or feeling like passing out • tiredness • fever			
COMMON			
Infections: • fever, sweats, or chills • nausea or flu-like symptoms • sore throat or difficulty swallowing • shortness of breath • diarrhea or stomach pain or cough		√	
RARE			
Complications of stem cell transplantation that uses donor stem cells (allogeneic) after treatment with POTELIGEO: These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

POTELIGEO vials must be stored under refrigeration at 2°C to 8°C in original package to protect from light until time of use.

Do NOT freeze. Do NOT shake.

Keep out of reach and sight of children.

If you want more information about POTELIGEO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.kyowakirin.ca, or by calling 1-844-768-3544.

This leaflet was prepared by Kyowa Kirin, Inc.

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