DRUG NAME: Mogamulizumab

SYNONYM(S): KW-0761[1], Mogamulizumab-kpkc[2]

COMMON TRADE NAME(S): POTELIGEO®

CLASSIFICATION: immunotherapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Mogamulizumab is a defucosylated, humanized IgG1κ monoclonal antibody which selectively binds to CC chemokine receptor 4 (CCR4). CCR4 is expressed on the surface of tumour cells in some T-cell malignancies, as well as on regulatory T-cells (Treg) and T helper cells (Th2). By binding to CCR4, mogamulizumab induces antibody-dependent cellular cytotoxicity (ADCC), resulting in cell apoptosis.[2-4]

PHARMACOKINETICS:

Distribution	limited extravascular distribution[5]	
	cross blood brain barrier?	no information found
	volume of distribution	3.6 L
	plasma protein binding	no information found
Metabolism	expected to undergo catabolism to small peptides and amino acids	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	eliminated by combination of target-mediated disposition and FcRN-mediated clearance[5]	
	urine	not expected due to the large molecular size [5]
	feces	no information found
	terminal half life	17 days
	clearance	12 mL/h
Sex	no clinically meaningful difference	
Elderly	no clinically meaningful difference	
Ethnicity	no clinically meaningful difference	

Adapted from standard reference [2-4] unless specified otherwise.

USES:

Primary uses:

*Lymphoma, cutaneous T-cell

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- fatal ***autoimmune complications*** have occurred with mogamulizumab; use cautiously in patients with history of autoimmune disease[3]
- ***infusion reactions*** may occur; premedication with diphenhydramine and acetaminophen is recommended prior to the first mogamulizumab infusion in all patients[3]
- serious ***infections*** have been reported; patients with concomitant systemic immunosuppressive agents may be at increased risk[5]
- ***tumour lysis syndrome (TLS)*** has been reported***;*** patients with rapidly proliferating tumour or high tumour burden may be at increased risk[3]
- ***reactivation of Hepatitis B virus*** has been reported with mogamulizumab[3]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***
- the safety and efficacy of ***vaccination*** in patients receiving immunotherapy is currently being investigated[6-9]

Carcinogenicity: No carcinogenicity studies have been conducted. Secondary malignancies, including squamous cell carcinoma, basal cell carcinoma, melanoma, and ovarian cancer have been reported.[3,10]

Mutagenicity: No studies have been conducted.

Fertility: No fertility studies have been conducted. In repeat-dose toxicity animal studies, no toxic effects were observed in male or female reproductive organs of sexually mature test subjects.[3]

Pregnancy: There is no available human data to inform a drug-associated risk. Human IgG is known to cross the placental barrier; therefore, mogamulizumab is expected to be transmitted from mother to fetus. In animal studies, mogamulizumab did not show a potential for embryo-fetal lethality, teratogenicity, or developmental toxicity. Although mogamulizumab was detected in fetal plasma and led to decreased CCR4-expressing lymphocytes in fetus, no abnormalities (external, visceral, or skeletal) were observed at exposures 27 times higher than those seen following human clinical exposure. For females of reproductive potential, contraception is recommended during treatment and for at least 6 months after the last dose.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be excreted in human breast milk. The potential effect of exposure on the breastfed infant is unknown.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[11,12]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (12-35%, severe 3%)[4]
	lymphocytopenia (5-31%, severe 5-16%)[4]
	leukopenia (severe 1%)[2]
	neutropenia (11%, severe 2%)
	thrombocytopenia (14-29%)[4]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	arrhythmia (5%)
	cardiac failure (<1%)
	myocardial ischemia/infarction (<1%)
	stress cardiomyopathy
eye	conjunctivitis (5%)
gastrointestinal	*emetogenic potential:* minimal (rare)[13]
	abdominal pain (7%)
	constipation (13%)
	diarrhea (30%)
	mucositis (14%, severe 1%)
	nausea (17%)
	vomiting (7%)
general disorders and administration site conditions	*extravasation hazard:* none[14]
	chills (7%)
	edema (17%)
	fatigue (31%)
	pyrexia (18%, severe <1%)
hepatobiliary	hepatitis (2%, severe <1%); see paragraph following **Side Effects** table
immune system (see paragraph following **Side Effects** table)	***autoimmune complications*** (severe <1% each); includes ***myositis, myocarditis, hepatitis, pneumonitis, Guillain-Barré syndrome, polymyositis, glomerulonephritis***
	hypothyroidism (1%); new onset, immune-mediated
	polymyalgia rheumatica
infections and infestations	candidiasis (9%)
	cellulitis (3%, severe 2%)
	cytomegalovirus infection (<1%)
	folliculitis (8%)
	herpes virus infection (5%); Hepatitis B virus reactivation reported
	lower respiratory tract infection (2%)
	otitis (5%)
	pneumonia (7%, severe 2%)[1]; fatalities reported
	pneumonitis (2%, severe <1%); see paragraph following **Side Effects** table
	sepsis (2%, severe 1%)[1]; fatalities reported
	skin infection (18%, severe 3%)
	upper respiratory tract infection (22%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	urinary tract infection (10%)
injury, poisoning, and procedural complications	fall (6%)
	infusion-related reaction (33%, severe 2%); see paragraph following **Side Effects** table
investigations	albumin decrease (36%, severe 3%)
	alkaline phosphatase increase (17%)
	ALT increase (19%, severe 2%)
	AST increase (26%, severe 2%)
	calcium decrease (30%, severe 3%)
	calcium increase (12%, severe <1%)
	CD4 T-cell lymphocytes decrease (40-63%, severe 25-43%)
	creatinine increase (3%)
	glucose decrease (15%, severe <1%)
	glucose increase (9-54%, severe 5%)
	magnesium decrease (19%, severe <1%)
	phosphate decrease (28%, severe 5%)
	potassium decrease (7%)
	uric acid increase (31%, severe 31%)
	white blood cells decrease (33%, severe 2%)
	weight gain (8%)
	weight loss (6%)
metabolism and nutrition	decreased appetite (9%)
	tumour lysis syndrome (<1%)
musculoskeletal and connective tissue	muscle spasm (5%)
	musculoskeletal pain (22%, severe <1%)
neoplasms	neoplasms (13%); includes benign and malignant neoplasms; incidence is higher in patients ≥65 years[3,10]
	adenocarcinoma (<1%)[1,10]
	basal cell carcinoma (3%)[10]
	malignant pleural effusion (<1%)[1,10]
	melanoma (<1%)[1,10]
	ovarian cancer (<1%)[1,10]
	squamous cell carcinoma (4%)[1,10]
nervous system	dizziness (9%)
	headache (15%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	peripheral neuropathy (7%)
psychiatric	depression (7%)
	insomnia (9%)
renal and urinary	glomerulonephritis; see paragraph following **Side Effects** table
	renal insufficiency (9%)
respiratory, thoracic and mediastinal	cough (13%)
	dyspnea (7%)
skin and subcutaneous tissue (see paragraph following **Side Effects** table)	alopecia (8%)
	rash*/*drug eruption (24-36%, severe 4-5%)
	Stevens-Johnson syndrome (<1%); fatalities reported
	toxic epidermal necrolysis (<1%); fatalities reported
	xerosis (9%)
vascular	hypertension (10%)

Adapted from standard reference[2-4] unless specified otherwise.

Dermatologic toxicity is commonly reported with mogamulizumab. The exact mechanism is not fully established. It is proposed that mogamulizumab-induced depletion of regulatory T cells may play a role.[15] The majority of skin reactions are grade 1 or 2. However, fatal cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported.[3] ***Drug eruption*** (i.e., mogamulizumab-associated rash[1]) occurs in 24% of patients and appearance may vary. The most common presentations are papular or maculopapular rash, lichenoid, and spongiotic or granulomatous dermatitis. Other reactions may include morbilliform rash, scaly plaques, pustular eruption, folliculitis, and psoriasiform dermatitis. Drug eruption in the scalp may result in hair loss.[16] Time to onset is variable. Median time to onset is 15 weeks[3] but reactions can occur even after treatment has ended.[16] Grade 2 or 3 events can be managed with dose interruption and corticosteroids. If SJS or TEN is suspected, withhold mogamulizumab until SJS/TEN has been ruled out and the reaction improves to grade 1 or less.[3] Skin biopsy is recommended to distinguish rash from disease progression. Dermatology consult may be required.[16] Permanently discontinue mogamulizumab for a grade 4 reaction.[3]

Autoimmune complications have occurred in patients receiving mogamulizumab. Some fatalities have been reported. Grade 3 or higher events include myositis, myocarditis, polymyositis, hepatitis, pneumonitis, glomerulonephritis, and Guillain-Barré syndrome. Systemic immunosuppressants may be required to manage events. Dose interruption or permanent discontinuation of mogamulizumab may be required based on severity of the event.[2,3]

Infusion-related reactions are reported in 35% of patients receiving mogamulizumab and can be severe in some cases. Reactions generally occur during or shortly after the first infusion (within 24 hours)[5], but can also occur with subsequent infusions. Symptoms include chills, nausea, fever, tachycardia, rigors, headache, and vomiting.[3] Premedication with diphenhydramine and acetaminophen is recommended for the first infusion in all patients. Withhold mogamulizumab for any grade reaction and treat symptoms promptly. Infusion may be resumed at a reduced rate (no more than 50% of the previous rate). If reaction recurs and is not manageable, discontinue infusion. Premedication should be administered for subsequent infusions. Permanently discontinue mogamulizumab for life-threatening (grade 4) reactions.[3] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents*.**

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Transplant complications such as acute or steroid-refractory graft versus host disease (GVHD) and transplant-related death have been reported in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) after mogamulizumab. The risk of complications appears to be higher when mogamulizumab is administered within 50 days prior to HSCT. Monitor for early evidence of transplant-related complications if HSCT is indicated.[3]

INTERACTIONS:

No known interactions.[3]

SUPPLY AND STORAGE:

***Injection*:** Kyowa Kirin Inc. (distributed by Innomar Strategies) supplies mogamulizumab as 20 mg vials of ready-to-use, single use (preservative free) solution in a concentration of 4 mg/mL. Refrigerate. Store in original carton to protect from light. Do not shake.[3]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	do NOT use[3]
Intramuscular	no information found
Direct intravenous	do NOT use[3]
Intermittent infusion[3]	***over 60 min***; administer using 0.22 micron in-line filter
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: ***4 weeks***[1,3]:	**Cycle 1:** ***1 mg/kg IV for one dose on days 1, 8, 15, and 22*** (total dose per cycle 4 mg/kg) **Cycle 2 and subsequent cycles:** ***1 mg/kg IV for one dose on days 1 and 15*** (total dose per cycle 2 mg/kg)
	Administer mogamulizumab within 2 days of the scheduled dose.[3]	
Concurrent radiation:	no information found	
Dosage in myelosuppression:	no information found	
Dosage in renal failure:	CrCl ≥30 mL/min: no adjustment required[3,5] CrCl <30 mL/min: no information found	
	calculated creatinine clearance =	N* x (140 - Age) x weight in kg serum creatinine in micromol/L
	* For males N=1.23; for females N=1.04	
Dosage in hepatic failure:	mild to moderate impairment (total bilirubin ≥1-3xULN): no adjustment required[3] severe impairment (total bilirubin >3xULN): no information found	
Dosage in dialysis:	no information found	

***Children*:** safety and efficacy not established

REFERENCES:

1. Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomized, controlled phase 3 trial. Lancet Oncol 2018;19(9):1192-1204
2. Kyowa Kirin Inc. POTELIGEO® full prescribing information. Bedminister, New Jersey, USA; March 30, 2022
3. Kyowa Kirin. POTELIGEO® product monograph. Oakville, Ontario; July 12, 2023
4. Lexi-Drugs® (database on the Internet). Mogamulizumab. Lexi-Comp Inc., 2023. Available at: http://online.lexi.com. Accessed 26 September, 2023
5. European Medicines Agency. Assessment Report - Mogamulizumab . Hoofddorp, The Netherlands; September 20 2018
6. Brest P, Mograbi B, Hofman P, et al. COVID-19 vaccination and cancer immunotherapy: should they stick together? Br J Cancer 2022;126(1):1-3
7. Chong C, Park VJ, Cohen B, et al. Safety of inactivated influenza vaccine in cancer patients receiving immune checkpoint inhibitors. Clin Infect Dis 2020;70(2):193-199

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8. Desage A, Bouleftour W, Rivoirard R, et al. Vaccination and immune checkpoint inhibitors: does vaccination increase the risk of immune-related adverse events? A systematic review of literature. Am J Clin Oncol 2021;44(3):109-113
9. Oosting SF, van der Veldt, A. A. M., GeurtsvanKessel CH, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. Lancet Oncol 2021;22(12):1681-1691
10. Sonish Azam. Senior Medical Science Liaison, Ocology. Personal Communication - mogamulizumab. October 27,2023
11. Kerry Savage MD. Medical oncologist, BC Cancer Lymphoma Tumour Group. Personal Communication. November 27,2023
12. Megan Darbyshire, Tumour Group Pharmacist. Provincial Pharmacy. Personal Communication. November 9,2023
13. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 2022
14. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; January 2016
15. AHFS Drug Information® (database on the Internet). Mogamulizumab. Lexi-Comp Inc., 2023. Available at: http://online.lexi.com. Accessed 26 September, 2023
16. Musiek ACM, Rieger KE, Bagot M, et al. Dermatologic Events Associated with the Anti-CCR4 Antibody Mogamulizumab: Characterization and Management. Dermatology and therapy 2022;12(1):29-40

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