DRUG NAME: Glofitamab

SYNONYM(S): Glofitamab-gxbm[1], RG 6026[2], RG6026-2[2], RO 7082859[2]

COMMON TRADE NAME(S): COLUMVI®

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Glofitamab is a bispecific T-cell engager that simultaneously binds to CD20 on B cells and CD3 receptors on T cells. It is a humanized immunoglobulin G1 (IgG1) monoclonal antibody. With its dual binding, glofitamab brings T cells in close contact with CD20 expressing B cells, initiating T cell activation and proliferation, release of cytokines, and subsequent cell lysis.[1,3]

PHARMACOKINETICS:

Absorption	T_{max} after single dose of 10 mg = 8 hrs	
Distribution	total volume of distribution: 5.6 L	
	cross blood brain barrier?	no information found
	volume of distribution	central Vd: 3.3 L; peripheral Vd: 2.2 L
	plasma protein binding	no information found
Metabolism	expected to be catabolized into small peptides and amino acids	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	biphasic clearance with both time-independent and time-varying clearance parameter	
	urine	no information found
	feces	no information found
	terminal half life	7.6 days at steady state[1] (range 4-8 days)
	clearance	0.6 L/day
Elderly	no clinically meaningful difference	

Adapted from standard reference[1,3,4] unless specified otherwise.

USES:

Primary uses:

*Lymphoma, non-Hodgkin

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- severe ***cytokine release syndrome*** (CRS) can occur with glofitamab; recommended dosing regimen uses a step-up dosing schedule for initiation of treatment[3]
- ***premedication*** is recommended prior to each dose of glofitamab[3]
- patients should be ***adequately hydrated*** prior to starting treatment[3]
- patients may experience ***reduced consciousness*** due to CRS and immune effector cell-associated neurotoxicity syndrome (ICANS); ***driving or operating heavy machinery*** should be avoided until symptoms resolve[3]
- avoid glofitamab in patients with ***active infection***; consider ***antimicrobial/antiviral prophylaxis*** for *Pneumocystis jirovecii pneumonia*, cytomegalovirus, and herpes virus reactivation in high risk patients[1,3]
- risk of ***tumour lysis syndrome*** is increased in patients with a high tumour burden, rapidly growing tumour, renal dysfunction, or dehydration[3]
- ***immunization with live virus vaccines*** is not recommended during glofitamab treatment[3]

Carcinogenicity: No studies have been conducted.

Mutagenicity: No studies have been conducted.

Fertility: No studies have been conducted.

Pregnancy: There is no human or animal data to evaluate associated risk in pregnancy. Cytokine release and immune activation triggered by glofitamab may compromise pregnancy maintenance. Prolonged B cell depletion during pregnancy can also increase the risk of opportunistic infections which may cause fetal loss. Because human IgG is known to cross the placental barrier, glofitamab is expected to cross from mother to fetus. Given the low transfer of antibodies during the first trimester and mechanism of action of glofitamab, the risk of teratogenicity is expected to be low. However, glofitamab may induce B cell depletion in infants exposed in utero. Pregnancy tests are recommended prior to starting treatment in females of reproductive potential and contraception is recommended during treatment and for 2 months after the last dose.[1,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Human IgG is known to be secreted in breast milk. Because of the potential for serious adverse reactions (e.g., B cell depletion) in breastfed infants, women should not breastfeed during treatment and for 2 months after the last dose.[1,3]

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.[5,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (28%, severe 7%)
	febrile neutropenia (3%)
	leukopenia (66%, severe 12%)
	lymphopenia (88%, severe 80%)
	neutropenia (34%, severe 24%)
	thrombocytopenia (24%, severe 6%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential:* minimal (rare)[7,8]
	abdominal pain (10%)
	constipation (12%)
	diarrhea (10%)
	nausea (9%)
	vomiting (3%)
general disorders and administration site conditions	*extravasation hazard:* none[9]
	fatigue (18%, severe 1%)
	edema (11%, severe 1%)
	pyrexia (18%)
immune system	***cytokine release syndrome*** (62%, severe 4%); see paragraph following **Side Effects** table
	hypogammaglobulinemia (1%)
infections and infestations (see paragraph following **Side Effects** table)	***bacterial infection*** (9%, severe 3%)
	COVID-19 pneumonia (3%, severe 2%); fatalities reported
	sepsis (4%, severe 1%); fatalities reported
	upper respiratory tract infection (5%)
	viral infection (11%, severe 3%)[3]; includes COVID 19, herpes zoster and cytomegalovirus infection[10]
injury, poisoning, and procedural complications	infusion-related reaction (4-6%)[10]; may be clinically indistinguishable from CRS
investigations	alkaline phosphatase increase (7%, severe 1%)
	ALT increase (8%, severe 3%)
	AST increase (7%, severe 3%)
	blood bilirubin increase (3%)
	fibrinogen decrease (84%, severe 21%)[1]
	gamma-glutamyltransferase increase (6%, severe 3%)
	glucose increase (12%, severe 12%)
	uric acid increase (21%, severe 21%)
metabolism and nutrition	hypocalcemia (13%)
	hypokalemia (11%, severe <1%)
	hypomagnesemia (13%)
	hyponatremia (8%, severe <1%)
	hypophosphatemia (18%, severe 6%)
	tumour lysis syndrome (severe 1%)[11]
musculoskeletal and connective tissue	arthralgia (6%)
	back pain (9%, severe 1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	musculoskeletal pain (21%, severe 2%)[1]
neoplasms	***tumour flare*** (11%, severe 3%); see paragraph following **Side Effects** table
nervous system (see paragraph following **Side Effects** table)	dizziness/vertigo (4-7%)
	headache (9-10%)
	immune effector cell-associated neurotoxicity syndrome (5%, severe 1%)[12]; fatalities reported
	mental status changes (5%); includes confusion, somnolence, and delirium[1]
	myelitis (severe 1%); occurred concurrently with CRS
	peripheral neuropathy (3-8%)
psychiatric	anxiety (4%)
skin and subcutaneous tissue	rash (14%, severe 1%)
vascular	gastrointestinal hemorrhage (3%)

Adapted from standard reference[1,3] unless specified otherwise.

Cytokine release syndrome (CRS) commonly occurs in patients receiving glofitamab. Most patients experience grade 1 or 2 reactions, but serious or life-threatening events can occur. Signs and symptoms of CRS may include fever, chills, hypoxia, hypotension, dyspnea, tachycardia, and elevated liver enzymes. Most events occur during cycle 1 and 2. CRS of any grade occurs in 54% of patients after the first step-up dose (2.5 mg), with a median onset time of 13 hours (range: 2-52 hours).[3] The first CRS event may also appear with the second step-up dose (10 mg). Median time to onset of CRS for subsequent doses during cycle 1 and 2 is 29 hours.[13] The incidence of CRS decreases with subsequent doses (e.g., 33% of patients after the 10 mg dose, 28% after the first 30 mg dose, and 1-2% for subsequent doses).[3] CRS resolves in most patients, with a median duration of 2 days (range 1-14 days). Recurrent CRS has been reported in 34% of patients. To reduce the risk of CRS, pretreatment with obinutuzumab is administered 7 days prior to the first dose of glofitamab to deplete the circulating and lymphoid B cells. Additionally, glofitamab is initiated with a step-up dosing regimen and premedication with antihistamine, antipyretic, and corticosteroid is recommended. If CRS is suspected, withhold glofitamab until symptoms resolve and manage symptoms promptly. Depending on severity of the reaction, management may include supportive care, corticosteroids, and tocilizumab. Consider slowing the infusion rate for subsequent doses. Permanently discontinue glofitamab for recurrent grade 3 reactions and all grade 4 reactions.[1,3] For management of cytokine release syndrome (CRS), see BC Cancer Protocol SCCRS ***Cytokine Release Syndrome Management*.**

Neurologic toxicity is reported in 40% of patients treated with glofitamab and includes headache, dizziness, anxiety, peripheral neuropathy, and mental status changes. Although most events are mild to moderate in severity, serious neurologic toxicity such as ***immune effector cell-associated neurotoxicity syndrome*** (ICANS) can occur, and fatalities have been reported. Clinical manifestations of ICANS may include headache, confusion, disorientation, speech disturbances, altered levels of consciousness, seizures, muscle weakness, agitation, and tremor. The median time to onset for ICANS is 8 days (range 1-106 days) from the first step-up dose (2.5 mg). The median duration of ICANS is 2 days (range 1-8 days). ICANS can occur concurrently with CRS, following the resolution of CRS, or in the absence of CRS.[12] Management of ICANS may include temporary dose interruption, corticosteroids, anti-seizure medications, and supportive care. Patients experiencing neurologic toxicity should avoid driving or operating heavy machinery until the symptoms resolve.[1] For inpatient management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), see BC Cancer Protocol SCICANS ***Immune Effector Cell-Associated Neurotoxicity Syndrome Management.***

Serious ***infections,*** including fatal cases of sepsis and COVID-19 pneumonia, have been reported in 17% of patients. Glofitamab should not be administered to patients with active infections. Patients with chronic or recurrent infections

and those with a history of significant prior immunosuppressive treatment may be at increased risk of serious infections. Antiviral/antibacterial prophylaxis for herpes zoster reactivation, cytomegalovirus infection, and/or *Pneumocystis jirovecii pneumonia* may be required.[1,3] Refer to protocol by which patient is being treated.

Tumour flare has been reported with glofitamab, likely due to the activated immune response and T cell influx towards tumour sites. Clinical presentation may include localized pain and swelling at lymphoma sites, tumour inflammation, and dyspnea from pleural effusion. Tumour flare does not indicate tumour progression. Patients with bulky tumours near airways or vital organs are at increased risk of complications such as organ compression, obstruction, or dysfunction. Most events occur during cycle 1, with median time to onset of 2 days. For events of grade 2 or higher severity, consider withholding glofitamab until tumour flare resolves. Management may include analgesics, antihistamine, corticosteroids and supportive care.[1,3]

INTERACTIONS:

Glofitamab causes transient elevation of cytokines and may suppress the activity of CYP450 enzymes, resulting in increased exposure of CYP substrates. Substrates of CYP450 enzymes with narrow therapeutic index may require dose adjustment or monitoring for toxicity if given concurrently with glofitamab. Interactions are most likely to occur after the first glofitamab administration, up to 14 days after the first 30 mg dose, as well as during/after a CRS event.[1,14]

SUPPLY AND STORAGE:

***Injection*:** Hoffmann-La Roche Ltd. supplies glofitamab as 2.5 mg and 10 mg ready-to-use, single-use (preservative free) vials in a concentration of 1 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.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	do NOT use
Intramuscular	do NOT use
Direct intravenous	do NOT use
Intermittent infusion[3,15]	cycle 1 and 2***: over 4 h*** cycle 3 and beyond***: over 2 h*** in-line filters are not required[3]; but may be used (e.g., 0.2 micron[1])
Continuous infusion	do NOT use
Intraperitoneal	do NOT use
Intrapleural	do NOT use
Intrathecal	do NOT use
Intra-arterial	do NOT use
Intravesical	do NOT use

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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: ***3 weeks***[3,11,15]:

Cycle 1:

Glofitamab Dosing Schedule		Day of treatment	Glofitamab Dose (IV)
Pretreatment with obinutuzumab		1	-
Step-up dosing schedule	Step-up dose 1	8	2.5 mg
	Step-up dose 2	15	10 mg

(total dose per cycle 12.5 mg)

Cycle 2 and beyond:
30 mg IV for one dose on day 1
(total dose per cycle 30 mg)

No dose reductions are recommended[3]

Following dose delays: for instruction about restarting glofitamab, refer to protocol by which patient is being treated as the step-up regimen and obinutuzumab pretreatment may need to be repeated[3]

Concurrent radiation: no information found

Dosage in renal failure: CrCl ≥30 mL/min: no adjustment required[1,3]
CrCl <30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: mild impairment (bilirubin ≤ 1.5 x ULN or AST >ULN): no adjustment required[1,3]
moderate/severe impairment: no information found

Dosage in dialysis: no information found

Children: safety and efficacy have not been established[3]

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