Drug Monograph

A - Drug Name

glofitamab

COMMON TRADE NAME(S): Columvi®

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B - Mechanism of Action and Pharmacokinetics

Glofitamab is a recombinant IgG1 bispecific, T-cell engaging monoclonal antibody. It binds bivalently to CD20 expressed on the surface of B cells and monovalently to CD3 expressed on the surface of T cells in a 2:1 tumour–T-cell binding configuration. Simultaneous binding to CD20 and CD3 mediates the formation of an immunological synapse which leads to potent T-cell activation and proliferation, and cytokine secretion that results in the lysis of CD20-expressing B cells.

Absorption	Glofitamab exhibits linear and dose-proportional pharmacokinetics	
	Peak plasma levels	concentration reaches the Cmax at the end of infusion and declines in a bi-exponential fashion
	T max	8 hours (after single 10mg dose)
Distribution	Cross blood brain barrier?	Unknown
	PPB	Unknown
Metabolism	Expected to be degraded into small peptides and amino acids via catabolic pathways	

Elimination		
	Two compartment model with both time-independent and time-varying clearance.	
	Half-life	7.6 days (at steady state)

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C - Indications and Status

Health Canada Approvals:

- Diffuse large B-cell lymphoma (DLBCL)
- Primary mediastinal B-cell lymphoma (PMBCL)

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- High grade B-cell lymphoma (HGBCL)
- Follicular lymphoma

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D - Adverse Effects

Emetogenic Potential: Minimal

The following adverse events were reported in a Phase I/ II study evaluating patients with relapsed or refractory DLBCL who received glofitamab monotherapy (following a single dose of obinutuzumab). Adverse effects were reported in ≥ 5% of patients; severe or life-threatening adverse events may also be included from the pivotal trial or other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	QT interval prolonged (7%)	E D
Dermatological	Rash, pruritus (14%) (1% severe)	E
Gastrointestinal	Abdominal pain (10%)	E
	Constipation (12%)	E

	Diarrhea (10%)	E
	GI hemorrhage (3%) (intestinal perforation < 1%)	E
	Nausea (9%)	E
General	Edema (11%)	E
	Fatigue (18%)	E
	Fever (18%)	I E
	Tumour flare (11%)	E
Hematological	Myelosuppression ± infection, bleeding (34%) (24% severe) (including new or reactivated viral infections)	E D
Hepatobiliary	↑ LFTs (8%) (3% severe)	E
Immune	Cytokine release syndrome (62%) (4% severe)	I E
	Other (1%) Hypogammaglobulinemia	E D
Metabolic / Endocrine	Abnormal electrolyte(s) (18%) (↓ PO4, ↓Mg, ↓Ca, ↓K, ↓Na) (6% severe)	E
	Tumour lysis syndrome (1%)	E
Musculoskeletal	Musculoskeletal pain (9%)	E
Nervous System	Headache (9%)	E
	Immune effector cell-associated neurotoxicity syndrome (8%)	I E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for glofitamab include cytokine release syndrome and myelosuppression ± infection.

Cytokine Release Syndrome (CRS) most commonly manifested as fever (almost all patients), tachycardia, hypotension, chills and hypoxia, and may be clinically indistinguishable from infusion-related reactions. Although cases of CRS were high in the pivotal trial (62%), most were Grade 1 (45%) or Grade 2 (13%), and all but one case resolved with management. Severe cases (Grade 3 or 4) were only reported in 4% of patients, and none were fatal. Events were most often following the first dose of glofitamab (54% of patients), but also observed after the second and third doses (33% and 28%, respectively). After Cycle 2, CRS events occurred more rarely (≤ 2% of patients) and no Grade ≥ 2 events were reported. The median time to onset was 13 hours after the first dose (range: 2.5 to 52 hours) and longer with subsequent doses (29 hours for dose 2 and 3). In patients with Grade ≥ 2 CRS, tocilizumab was administered to 88%, corticosteroids to 60%, and both tocilizumab and corticosteroids to 56% of patients. Pre-treatment with obinutuzumab, pre-medications and a step-up dosing schedule were given in clinical trial to reduce the occurrence and severity of CRS.

The incidence of **serious Infections** in patients receiving glofitamab was 17%, which included some fatal cases (4%). The most frequently reported infections were sepsis, pneumonia and COVID-19. Febrile neutropenia occurred in 3% of patients. Antimicrobial prophylaxis should be administered according to local guidelines and patients should be monitored and treated appropriately.

Tumour flare manifestations include localized pain and swelling at the sites of lymphoma lesions and tumour inflammation, likely due to the influx of T-cells into tumour sites following glofitamab administration. Those reported in the clinical trial involved lymph nodes in the head and neck, and thorax, and presented with pain (head & neck) or breathlessness (thorax). Most tumour flare events occurred during Cycle 1 (94%), and no events were reported beyond Cycle 2. Onset was 2 days (range: 1 to 16) and lasted 3.5 days (range: 1 to 35 days). Although it may mimic disease progression, tumour flare does not imply treatment failure or represent tumour progression.

Tumour lysis syndrome (TLS) has been reported in 2 patients (1.3%) receiving glofitamab and both cases were severe (Grade 3). Onset was 2 days (median time) and resolved in 4 days (range: 3 to 5). Those at greater risk include patients with high tumour burden, rapidly proliferating tumours and renal dysfunction or dehydration. Appropriate prophylactic medications should be considered prior to administering glofitamab (e.g. hydration and allopurinol or rasburicase).

Glofitamab may cause serious **neurological toxicities**, such as immune effector cell-associated neurotoxicity syndrome (ICANS). Neurological toxicities were reported in 36% of patients; however, the majority were mild (Grade 1 or 2). The most frequently reported neurological effects in trials were headache, dizziness, anxiety, and paresthesia. Somnolence, tremor, myelitis, and confusion were less commonly reported (≤ 2%), and some events occurred concurrently with CRS. Grade ≥ 3 neurologic events included somnolence, agitation, delirium, and myelitis and occurred in a small percentage of patients.

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E - Dosing

Refer to protocol by which the patient is being treated.

Do not start treatment with glofitamab in patients with active infection.

Must have tocilizumab available prior to starting glofitamab (Cycles 1 and 2).

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Pre-medications (prophylaxis for CRS):

Cycles 1 to 3:

Give at least 30 min to 1 hr prior to each glofitamab infusion:

- IV glucocorticoid* (e.g. dexamethasone 20 mg or equivalent)
- Antihistamine (e.g. diphenhydramine 50 mg PO/IV)
- Antipyretic (e.g. acetaminophen 1000 mg PO)

Cycle 4 and beyond:

Give at least 30 min prior to each glofitamab infusion**:**

- Antihistamine (e.g. diphenhydramine 50 mg PO/IV)
- Antipyretic (e.g. acetaminophen 1000 mg PO)
- Add IV glucocorticoid* **for patients who experienced CRS with previous doses**

*Glucocorticoid to be completed at least 1 hour before each glofitamab infusion.

Other Supportive Care:

- Consider prophylaxis against Pneumocystis jirovecii pneumonia (PJP) and herpes virus infections.
- Consider other antimicrobial prophylaxis as per local guidelines.
- Glofitamab should be administered to adequately hydrated patients.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Adults:

All patients should receive a single obinutuzumab dose prior to starting glofitamab to deplete circulating and lymphoid tissue B cells and minimize the risk of CRS. Glofitamab should also be administered according to a step-up schedule to reduce the risk of CRS.

Cycle 1 (21 days):

	Day of Treatment	**Glofitamab Dose (mg, IV)**
Pre-treatment	1	Pre-treatment with obinutuzumab*
Step-up dose 1	8	2.5
Step-up dose 2	15	10

*Refer to GLOF regimen monograph and obinutuzumab product monograph for dosing, pre-

medications, and administration information.

Cycles 2 to 12:

IV: 30 mg on Day 1, q 21 days

Note: Inpatient admission may be required for CRS monitoring. ST-QBP funding for ambulatory administration only.

Dosage with Toxicity:

Dose reductions are not recommended.

Table 1 - CRS Toxicity Management

Recommendations below are based on the product monograph. Refer to Crombie et al. for alternative CRS management guidelines.

Toxicity	Grade[a]	Management / Action	Next dose[c]
CRS	Grade 1	• Hold until CRS has resolved. • Manage and treat symptoms as appropriate[b]. If CRS lasts more than 48 h after symptomatic management: ◦ Consider corticosteroids (e.g. dexamethasone 10 mg IV, or equivalent) ◦ Consider tocilizumab IV as per institutional guidelines. • Refer to Table 5 for recommendations on infusion rates, restart and re-challenge.	Resume dose as recommended in Table 4.
	Grade 2	• Hold. • Manage and treat symptoms as appropriate[b]: ◦ Corticosteroids (e.g. dexamethasone 10 mg IV, or equivalent) ◦ Consider tocilizumab IV as per institutional guidelines. • Refer to Table 5 for	Resume dose as recommended in Table 4. Monitor patient more frequently following dose; consider hospitalization.

		recommendations on infusion rates, restart and re-challenge.	
	Grade 3	• Hold. • Manage and treat symptoms as appropriate[b]: ◦ Corticosteroids (e.g. dexamethasone 10 mg IV, or equivalent) ◦ Tocilizumab IV as per institutional guidelines. • Refer to Table 5 for recommendations on infusion rates, restart and re-challenge.	Resume dose as recommended in Table 4. Hospitalize for monitoring following dose.
	Recurrent Grade 3, or Grade 4	• Stop glofitamab. • Manage and treat symptoms as appropriate[b]: ◦ Corticosteroids (e.g. dexamethasone 10 mg IV, or equivalent) ◦ Tocilizumab IV as per institutional guidelines.	Permanently discontinue.

[a] Grade based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Lee et al 2019).

[b] Anticytokine therapy is recommended if ICANS occurs concurrently with CRS. Refer to local institutional guidelines for management of concurrent CRS and ICANS.

[c] Do not give next dose unless symptoms have resolved for at least 72 hours.

Table 2 - Neurologic Toxicity

Severity[a]	**Action[b,c]**
Grade 1	Continue glofitamab and monitor for neurologic toxicity.
Grade 2	Hold[d,e] until neurologic toxicity improves to Grade ≤ 1 or baseline. Manage and treat symptoms as appropriate. Consider neurology consultation.
Grade 3	Hold[d] until neurologic toxicity improves to Grade ≤ 1 or baseline for ≥ 7 days.

	Consider permanently discontinuing for Grade 3 events lasting > 7 days. Manage and treat symptoms as appropriate. Consider neurology consultation.
Grade 4	Permanently discontinue. Manage and treat symptoms as appropriate. Consider neurology consultation.

[a] Grade for ICANS based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Lee et al 2019).

[b] If ICANS, manage as per institutional guidelines. Refer also to Crombie et. al for alternative ICANS management guidelines.

[c] Anticytokine therapy is recommended if ICANS occurs concurrently with CRS. Refer to local institutional guidelines for management of concurrent CRS and ICANS.

[d] Resume at dose described in Table 4.

[e] Consider the type of neurologic toxicity before deciding to withhold glofitamab.

Table 3 - Other Toxicities

Toxicity	**Severity**	**Action**
Active Infection	Grade 1 to 3	Hold* until infection resolves.
	Grade 4	Hold* until infection resolves, OR Consider discontinue.
Tumour flare	Grade 1	Monitor for signs and symptoms of compression or obstruction due to mass effect**.
	Grade 2 to 4	Hold* until tumour flare resolves. Monitor for signs and symptoms of compression or obstruction due to mass effect**. Initiate appropriate treatment (e.g. antihistamine and corticosteroids). Consider discontinue for Grade 4.
Neutropenia	ANC < 0.5 × 10^9/L	Hold* until ANC ≥ 0.5 × 10^9/L.
Thrombocytopenia	Platelets < 50 × 10^9/L	Hold* until platelets ≥ 50 × 10^9/L.
Other adverse	Grade ≥ 3	Hold* until toxicity improves to Grade ≤ 1 or baseline.

effects		

*Resume at dose described in Table 4.

**Especially in patients with bulky tumours located in close proximity to airways and/or vital organs.

Table 4 - Restarting After Dose Delay

Last Administered Dose	Time since Last Dose	Action for Next Dose
Obinutuzumab pre-treatment (Cycle 1, Day 1)	≤ 2 weeks	Administer glofitamab 2.5 mg, then resume the planned treatment schedule.
	> 2 weeks	Repeat pre-treatment with obinutuzumab, then resume the planned treatment schedule.
Glofitamab 2.5 mg (Cycle 1, Day 8)	≤ 2 weeks	Administer glofitamab 10 mg, then resume the planned treatment schedule.
	> 2 to ≤ 6 weeks	Repeat glofitamab 2.5 mg, then resume the planned treatment schedule.
	> 6 weeks	Repeat pre-treatment with obinutuzumab and glofitamab 2.5 mg, then resume the planned treatment schedule.
Glofitamab 10 mg (Cycle 1, Day 15)	≤ 2 weeks	Administer glofitamab 30 mg, then resume the planned treatment schedule.
	> 2 to ≤ 6 weeks	Repeat glofitamab 10 mg, then resume the planned treatment schedule.
	> 6 weeks	Repeat pre-treatment with obinutuzumab and step-up doses, then resume the planned treatment schedule.
Glofitamab 30 mg (Cycle 2 onwards)	≤ 6 weeks	Administer glofitamab 30 mg, then resume the planned treatment schedule.
	> 6 weeks	Repeat pre-treatment with obinutuzumab and step-up doses, then resume the planned treatment schedule.

Table 5 - Management of Infusion-related reactions (including CRS):

Refer to oBINutuzumab drug monograph for management of infusion-related reactions with obinutuzumab pre-treatment.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge*
1	• Stop the infusion. • Manage the symptoms. **Restart:** • After symptoms resolve, restart infusion at a slower rate (up to 50% slower, or up to 8 hr duration).	• Consider slower infusion rate (up to 50% slower, or up to 8 hr duration).
2	• Stop the infusion. • Manage the symptoms. • Do not restart.	• Consider slower infusion rate (up to 50% slower, or up to 8 hr duration). • Monitor patients post-infusion.
3	• Stop the infusion. • Aggressively manage the symptoms. • Do not restart.	• Consider slower infusion rate (up to 50% slower, or up to 8 hr duration). • Monitor patients post-infusion. • If Grade ≥ 3 CRS recurs, stop infusion immediately and permanently discontinue.
4	• Stop treatment. • Aggressively manage the symptoms. • Do not restart.	• Permanently discontinue (do not re-challenge).

* Ensure symptoms are resolved for at least 72 hours prior to next infusion.

Dosage with Hepatic Impairment:

No dose adjustment is necessary for mild hepatic impairment based on pharmacokinetic studies (no clinically significant differences observed). Glofitamab has not been studied in patients with moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST).

Dosage with Renal Impairment:

No dose adjustment is necessary in patients with mild or moderate renal impairment (CrCl 30 to < 90 mL/min). No clinically significant changes in the pharmacokinetics of glofitamab were observed based on mild to moderate renal impairment. The effects of severe renal impairment (CrCl 15 to < 30 mL/min) and end-stage renal disease (CrCl < 15 mL/min) on the pharmacokinetics of glofitamab are unknown.

Dosage in the elderly:

No dose adjustment is required in patients ≥ 65 years of age. No differences in safety or efficacy of glofitamab were observed between patients ≥ 65 years of age and those under 65 years.

Dosage based on gender:

No clinically significant changes in the pharmacokinetics of glofitamab were observed based on sex.

Children:

The safety and efficacy of glofitamab in pediatric patients (age < 18) have not been established.

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F - Administration Guidelines

- Infuse IV through a dedicated line. Do NOT administer as an IV push or bolus.
- Do not mix with other drugs.
- Dilute in a 50mL or 100mL 0.9% or 0.45% sodium chloride infusion bag.
- Final drug concentration after dilution should be 0.1 mg/mL to 0.6 mg/mL.
- Gently invert infusion bag to mix. Do not shake.
- Compatible with polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP), or non-PVC polyolefin 0.9% NS IV bags and PVC 0.45% sodium chloride IV bags.
- Compatible with infusion sets with product-contacting surfaces of polyurethane, PVC, PE, and in-line filter membranes made of polyethersulfone or polysulfone
- Infuse IV over 4 hours (2.5 mg, 10mg and first 30mg dose).
- May infuse over 2 hours (Cycle 3 and onwards) if previous dose well tolerated.
- Monitor patients during infusion, for 10 hours after the first glofitamab dose (2.5mg, Cycle 1, Day 8) and after subsequent doses as necessary, for signs and symptoms of CRS or ICANS.
- Store unopened vials refrigerated (2°C to 8°C) and protect from light.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any of its components.

Other Warnings/Precautions:

- Serious and life-threatening CRS have occurred with glofitamab; ensure step-up schedule is followed and infusions are administered where there is immediate access to medications and equipment required to manage CRS.
- Patients with an active infection should not receive glofitamab.
- Exercise caution when considering glofitamab in patients with:
  - a history of chronic or recurrent infection;
  - underlying conditions that may predispose them to infections;
  - significant prior immunosuppressive treatment.
- Live vaccines should not be administered during treatment with glofitamab. The safety of immunization with live vaccines during or after glofitamab treatment has not been studied.
- Symptoms of CRS (e.g. tachycardia, hypotension, hypoxia) or neurologic effects may affect ability to drive or operate machinery. Patients should avoid driving or operating machinery until symptoms resolve.
- Patients with high tumour burden, rapidly proliferative tumours, renal dysfunction or dehydration are at greater risk of tumour lysis syndrome.
- Patients with conditions such as central nervous system lymphoma, prior allogeneic HSCT and autoimmune disease (requiring immunosuppressive therapy) were excluded from clinical trials; assess benefit-risk of glofitamab treatment in these patients.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Fetotoxicity: Unknown
  IgG is known to cross the placenta. Glofitamab is likely to cause fetal B-cell depletion when administered to a pregnant woman, based on MOA. Opportunistic infection due to prolonged B-cell depletion may cause fetal loss. CRS associated with treatment may also be harmful to fetus.
- Teratogenicity: Unknown
  Risk is low based on low placental transfer of antibodies during first trimester, mechanism of action of glofitamab and data on other anti-CD20 antibodies.
- Pregnancy:
  Glofitamab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **2 months** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **2 months** after the last dose.
- Excretion into breast milk: Unknown
  Human IgG is known to be present in human milk. The potential for absorption of glofitamab and the potential for adverse reactions in the infant is unknown.
- Fertility effects: Unknown

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H - Interactions

Glofitamab causes a transient release of interleukin-6 levels that may suppress CYP450 enzymes, resulting in an increased exposure to CYP substrates. PK models suggest the magnitude of effect on CYP activities is < 50% and changes in exposure to CYP3A4, CY1A2 and CYP2C9 substrates may be ≤ 2x. Monitor patients receiving concomitant CYP450 substrates, especially those that have a narrow therapeutic index, for increased substrate concentrations or toxicity.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↑ substrate concentration and/or toxicity	cytokines released may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic index (e.g. warfarin) if necessary
CYP3A4 substrates (e.g. cyclosporine,	↑ substrate concentration and/or toxicity	cytokines released may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic

pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	index (e.g. cyclosporine) if necessary

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose; more frequently if clinically indicated
Clinical toxicity assessment for CRS	At each visit and for 10 hours after the first glofitamab infusion
Renal function tests	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated
CRP, ferritin, coagulation tests (e.g. aPTT, INR, PT, fibrinogen)	Baseline and as clinically indicated
Electrolytes (e.g. PO4, K, Ca and Mg), uric acid levels	As clinically indicated, especially for patients at risk of TLS
Clinical toxicity assessment for infection, TLS, rash, tumour flare, bleeding, neurologic (including ICANS), pulmonary, cardiac and GI toxicity.	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

High Cost Therapy Funding Program

- Glofitamab (Inpatient) - Relapsed or Refractory Diffuse Large B-cell Lymphoma

New Drug Funding Program (NDFP Website)

- Glofitamab (Outpatient) - Relapsed or Refractory Diffuse Large B-cell Lymphoma

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K - References

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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