Medicines & Healthcare products Regulatory Agency

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and the information is provided to assist physicians in prescribing this medicine outside the licence. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine in this new promising indication. As such, this is a scientific opinion and should not be regarded as an indication licensed by the MHRA or a future commitment by the MHRA to license such an indication, nor should it be regarded as an authorisation to sell or supply a medicine for such an indication. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

1. NAME OF THE MEDICINAL PRODUCT

Glofitamab 10 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glofitamab 10 mg concentrate for solution for infusion
Each vial of 10 mL contains 10 mg of glofitamab at a concentration of 1 mg/mL.

Glofitamab is a humanized anti-CD20 anti-CD3 bispecific monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion sterile concentrate)

Colourless, clear solution with a pH of 5.5 and osmolality of 270-350 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Glofitamab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.

4.2 Posology and method of administration

Glofitamab must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients and who has access to appropriate medical support to manage severe reactions associated with cytokine release syndrome (CRS).

At least 1 dose of tocilizumab for use in the event of CRS must be available prior to glofitamab infusion,at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured (see section 4.4).

Pre-treatment with obinutuzumab

All patients in study NP30179 received a single 1 000 mg dose of obinutuzumab as pre-treatment on Cycle 1 Day 1 (7 days prior to initiation of glofitamab treatment) to lower the circulating and lymphoid B cells to reduce the risk of CRS (see Table 2, *Delayed or Missed Doses*, and section 5.1).

Obinutuzumab was administered as an intravenous infusion at 50 mg/h. The rate of infusion was escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Refer to the obinutuzumab prescribing information for complete information on premedication, preparation, administration and management of adverse reactions of obinutuzumab.

Premedication and prophylactic medications

Cytokine release syndrome prophylaxis

Glofitamab should be administered to well-hydrated patients. Premedication to reduce the risk of CRS (see section 4.4) is outlined in Table 1.

Table 1. Premedication before glofitamab infusion to reduce the risk of cytokine release syndrome

Treatment Cycle (Day)	Patients requiring premedication	Premedication	Administration
Cycle 1 (Day 8, Day 15); Cycle 2 (Day 1); Cycle 3 (Day 1)	All patients	Intravenous glucocorticoid[1]	Completed at least 1 hour prior to glofitamab infusion
		Oral analgesic / anti-pyretic[2]	At least 30 minutes before glofitamab infusion
		Anti-histamine[3]	
All subsequent infusions	All patients	Oral analgesic / anti-pyretic[2]	At least 30 minutes before glofitamab infusion
		Anti-histamine[3]	
	Patients who experienced CRS with previous dose	Intravenous glucocorticoid[1,4]	Completed at least 1 hour prior to glofitamab infusion

[1] 20 mg dexamethasone or 100 mg prednisone/prednisolone or 80 mg methylprednisolone.
[2] For example, 1 000 mg paracetamol.
[3] For example, 50 mg diphenhydramine.
[4] To be administered in addition to the premedication required for all patients.

Posology

Glofitamab dosing begins with a step-up dosing schedule (which is designed to decrease the risk of CRS), leading to the recommended dose of 30 mg.

Glofitamab dose step-up schedule

Glofitamab must be administered as an intravenous infusion according to the dose step-up schedule leading to the recommended dose of 30 mg (as shown in Table 2), after completion of pre-treatment with obinutuzumab on Cycle 1 Day 1. Each cycle is 21 days.

Table 2. Glofitamab monotherapy dose step-up schedule for patients with relapsed or refractory DLBCL

Treatment cycle, Day		Dose of glofitamab	Duration of infusion
Cycle 1 (Pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab[1]	
	Day 8	2.5 mg	4 hours[2]
	Day 15	10 mg	
Cycle 2	Day 1	30 mg	
Cycle 3 to 12	Day 1	30 mg	2 hours[3]

[1] Refer to "*Pre-treatment with obinutuzumab*" described above.
[2] For patients who experience CRS with their previous dose of glofitamab, the duration of infusion may be extended up to 8 hours (see section 4.4).
[3] At the discretion of the treating physician, if the previous infusion was well tolerated. If the patient experienced CRS with a previous dose, the duration of infusion should be maintained at 4 hours.

Patient monitoring

- All patients must be monitored for signs and symptoms of potential CRS during infusion and for at least 24 hours after completion of the infusion of the first glofitamab dose (2.5 mg on Cycle 1 Day 8). The prescriber should use the information on CRS times to onset and grade after each dose, provided in Section 4.8, when determining the appropriate monitoring strategy, according to local guidelines and

policies

- Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of the infusion. See Table 3.

All patients must be counselled on the risk, signs and symptoms of CRS and advised to contact the healthcare provider immediately should they experience signs and symptoms of CRS. See section 4.4.

Duration of treatment

Treatment with glofitamab is recommended for a maximum of 12 cycles unless a patient experiences unmanageable toxicity or disease progression. Each cycle is 21 days.

Delayed or missed doses

During step-up dosing (weekly dosing):

- Following pre-treatment with obinutuzumab, if the glofitamab 2.5 mg dose is delayed by more than 1 week, then repeat pre-treatment with obinutuzumab.

- Following glofitamab 2.5 mg dose or 10 mg dose, if there is a glofitamab treatment-free interval of 2 weeks to 6 weeks, then repeat the last tolerated glofitamab dose and resume the planned step-up dosing.

- Following glofitamab 2.5 mg dose or 10 mg dose, if there is a glofitamab treatment-free interval of more than 6 weeks, then repeat pre-treatment with obinutuzumab and glofitamab step-up dosing (see Cycle 1 in Table 2).

After Cycle 2 (30 mg dose):

- If there is a glofitamab treatment-free interval of more than 6 weeks between cycles, then repeat pre-treatment with obinutuzumab and glofitamab step-up dosing (see Cycle 1 in Table 2), and then resume the planned treatment cycle (30 mg dose).

Dose modifications

No dose reductions of glofitamab are recommended. Adverse events should be managed with dose interruption, treatment discontinuation and reduction of the infusion rate (see 'Delayed or missed doses' and 'Management of cytokine release syndrome').

Management of Cytokine Release Syndrome (CRS)

CRS should be identified based on the clinical presentation (see sections 4.4 and 4.8). Patients should be evaluated for other causes of fever, hypoxia, and hypotension, such as infections or sepsis. If CRS is suspected, it should be managed according to the CRS management recommendations based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading in Table 3.

Table 3. ASTCT CRS grading and CRS management guidance

Grade[1]	**CRS management**	**For next scheduled glofitamab infusion**
Grade 1 Fever ≥ 38 °C	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Restart infusion at slower rate when symptoms resolve	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[2]

	• If symptoms recur, discontinue current infusion If CRS occurs post-infusion: • Treat symptoms If CRS lasts more than 48 h after symptomatic management: • Consider corticosteroids[3] • Consider tocilizumab[4]	
Grade 2 Fever ≥ 38 °C and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen by nasal cannula or blow-by	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Administer corticosteroids[3] • Consider tocilizumab[4] If CRS occurs post-infusion: • Treat symptoms • Administer corticosteroids[3] • Consider tocilizumab[4]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[2] • Monitor patients post-infusion[5, 6]
For Grade 2: Tocilizumab use Do not exceed 3 doses of tocilizumab in a period of 6 weeks. If no prior use of tocilizumab or if 1 dose of tocilizumab was used within the last 6 weeks: • Administer first dose of tocilizumab[4] • If no improvement within 8 hours administer second dose of tocilizumab[4] • After 2 doses of tocilizumab, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy If 2 doses of tocilizumab were used within the last 6 weeks: • Administer only one dose of tocilizumab[4] • If no improvement within 8 hours consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy		
Grade [1]	**CRS management**	**For next scheduled glofitamab infusion**
Grade 3 Fever ≥ 38 °C and/or hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Administer corticosteroids[3] • Administer tocilizumab[4] If CRS occurs post-infusion: • Treat symptoms • Administer corticosteroids[3] Administer tocilizumab[4]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[2] • Monitor patients post-infusion[5, 6] • If Grade ≥ 3 CRS recurs at subsequent infusion, stop infusion immediately and permanently discontinue glofitamab

Grade 4 Fever ≥ 38 °C and/or hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	If CRS occurs during infusion or post-infusion: • Permanently discontinue glofitamab and treat symptoms • Administer corticosteroids[3] • Administer tocilizumab[4]

For Grade 3 and Grade 4: Tocilizumab use
Do not exceed 3 doses of tocilizumab in a period of 6 weeks.

If no prior use of tocilizumab or if 1 dose of tocilizumab was used within the last 6 weeks:
- Administer first dose of tocilizumab[4]
- If no improvement within 8 hours or rapid progression of CRS, administer second dose of tocilizumab[4]
- After 2 doses of tocilizumab, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy

If 2 doses of tocilizumab were used within the last 6 weeks:
- Administer only one dose of tocilizumab[4]
- If no improvement within 8 hours or rapid progression of CRS, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy

[1] American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria (Lee DW et al ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-38).
[2] Duration of infusion may be extended up to 8 hours, as appropriate for that cycle (see Table 2).
[3] Corticosteroids (e.g., 10 mg intravenous dexamethasone, 100 mg intravenous prednisolone, 1-2 mg/kg intravenous methylprednisolone per day, or equivalent).
[4] Tocilizumab 8 mg/kg intravenously (not to exceed 800 mg).
[5] In Study NP30179, Grade ≥ 2 CRS following glofitamab 10 mg dose at Cycle 1 Day 15 occurred in 5.2% of patients, with a median time to onset of 26.2 hours from the start of infusion (range: 6.7 to 144.2 hours).
[6] In Study NP30179, Grade ≥ 2 CRS following glofitamab 30 mg dose at Cycle 2 Day 1 occurred in one patient (0.8%), with a time to onset of 15.0 hours from the start of infusion.

Special populations

Elderly
No dose adjustment is required in patients 65 years of age and older (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (total bilirubin > upper limit of normal [ULN] to ≤ 1.5 × ULN or aspartate transaminase [AST] > ULN). Glofitamab has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min). glofitamab has not been studied in patients with severe renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of glofitamab in children below 18 years of age have not been established. No data are available.

Method of administration

Glofitamab is for intravenous use only.

Glofitamab must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration. It must be administered as an intravenous infusion through a dedicated infusion line.

Glofitamab must not be administered as an intravenous push or bolus.

For instructions on dilution of glofitamab before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to obinutuzumab or to any of the excipients listed in section 6.1.

For specific contraindications on obinutuzumab, please refer to the obinutuzumab prescribing information.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Cytokine release syndrome

CRS, including life-threatening reactions, has been reported in patients receiving glofitamab (see section 4.8).

The most common manifestations of CRS were pyrexia, tachycardia, hypotension, chills and hypoxia. Infusion-related reactions may be clinically indistinguishable from manifestations of CRS.

Most CRS events occurred following the first dose of glofitamab. Elevated liver function tests (AST and alanine transaminase [ALT] > 3 x ULN and/or total bilirubin > 2 x ULN) concurrent with CRS have been reported after glofitamab use (see section 4.8).

Patients in study NP30179 were pre-treated with obinutuzumab, 7 days prior to initiation of glofitamab therapy, and patients should be premedicated with an anti-pyretic, antihistamine and a glucocorticoid (see section 4.2).

At least 1 dose of tocilizumab for use in the event of CRS must be available prior to glofitamab infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.

Patients must be monitored during all glofitamab infusions and for at least 24 hours after completion of the first infusion. The prescriber should use the information on CRS times to onset and grade after each dose, provided in Section 4.8, when determining the appropriate monitoring strategy, according to local guidelines and policies. For complete information on monitoring, see section 4.2. Patients must be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time (see Patient Card below).

Patients should be evaluated for other causes of fever, hypoxia and hypotension, such as infections or sepsis. CRS should be managed based on the patient's clinical presentation and according to the CRS management guidance provided in Table 3.

Glofitamab should be withheld until CRS resolves or permanently discontinued based on severity.

Patient card

The prescriber must inform the patient of the risk of CRS and signs and symptoms of CRS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS. Patients should

be provided with the patient card and instructed to carry the card at all times. This card describes symptoms of CRS which, if experienced, should prompt the patient to seek immediate medical attention.

Serious infections

Serious infections (such as sepsis and pneumonia) have occurred in patients treated with glofitamab (see section 4.8).

Glofitamab must not be administered to patients with an active infection. Caution should be exercised when considering the use of glofitamab in patients with a history of chronic or recurrent infection, those with underlying conditions that may predispose them to infections, or those who have had significant prior immunosuppressive treatment. Patients should be monitored before and during glofitamab treatment for the emergence of possible bacterial, fungal, and new or reactivated viral infections and treated appropriately.

Glofitamab should be temporarily withheld in the presence of an active infection until the infection has resolved. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur.

Febrile neutropenia has been reported during treatment with glofitamab. Patients with febrile neutropenia should be evaluated for infection and treated promptly.

Tumour flare

Tumour flare has been reported in patients receiving glofitamab (see section 4.8). Manifestations included localised pain and swelling.

Consistent with the mechanism of action of glofitamab, tumour flare is likely due to the influx of T cells into tumour sites following glofitamab administration and may mimic progression of disease. Tumour flare does not imply treatment failure or represent tumour progression.

Specific risk factors for tumour flare have not been identified, however, there is a heightened risk of compromise and morbidity due to mass effect secondary to tumour flare in patients with bulky tumours located in close proximity to airways and/or a vital organ. Monitoring and evaluation for tumour flare at critical anatomical sites is recommended in patients treated with glofitamab and managed as clinically indicated. Corticosteroids and analgesics should be considered to treat tumour flare.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported in patients receiving glofitamab (see section 4.8). Patients with high tumour burden, rapidly proliferative tumours, renal dysfunction or dehydration are at greater risk of tumour lysis syndrome.

Patients at risk should be monitored closely by appropriate laboratory and clinical tests for electrolyte status, hydration and renal function. Appropriate prophylactic measures with anti-hyperuricaemics (e.g., allopurinol or rasburicase) and adequate hydration should be considered prior to obinutuzumab pre-treatment and prior to glofitamab infusion.

Management of TLS may include aggressive hydration, correction of electrolyte abnormalities, anti-hyperuricaemic therapy and supportive care.

Immunisation

The safety of immunisation with live vaccines during or following glofitamab therapy has not been studied. Immunisation with live vaccines is not recommended during glofitamab therapy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No interactions with glofitamab are expected via the cytochrome P450 enzymes, other metabolizing enzymes or transporters.

The initial release of cytokines associated with the start of glofitamab treatment could suppress CYP450 enzymes. The highest drug-drug interaction risk is during the period of one week following each of the first 2 doses of glofitamab (i.e., Cycle 1 Day 8 and 15) in patients who are receiving concomitant CYP450 substrates with a narrow therapeutic index (e.g., warfarin, cyclosporine). On initiation of glofitamab therapy, patients being treated with CYP450 substrates with a narrow therapeutic index should be monitored as fluctuations in the concentration of concomitant drugs may lead to toxicity, loss of effect or adverse events.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Female patients of childbearing potential must use highly effective contraceptive methods during treatment with glofitamab and for at least 2 months following the last dose of glofitamab.

Pregnancy

There are no data on the use of glofitamab in pregnant women. No reproductive toxicity studies have been performed in animals (see section 5.3).

Glofitamab is an immunoglobulin G (IgG). IgG is known to cross the placenta. Based on its mechanism of action, glofitamab is likely to cause foetal B-cell depletion when administered to a pregnant woman.

Glofitamab is not recommended during pregnancy and in women of childbearing potential not using contraception. Female patients receiving glofitamab should be advised of the potential harm to the foetus. Female patients should be advised to contact the treating physician, should pregnancy occur.

Breast-feeding

It is not known whether glofitamab is excreted in human milk. No studies have been conducted to assess the impact of glofitamab on milk production or its presence in breast milk. Human IgG is known to be present in human milk. The potential for absorption of glofitamab and the potential for adverse reactions in the nursing infant is unknown. Women should be advised to discontinue breast-feeding during treatment with glofitamab and for 2 months after the final dose of glofitamab.

Fertility

No fertility assessments in animals have been performed to evaluate the effect of glofitamab on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Glofitamab has minor influence on the ability to drive and use machines. Patients experiencing symptoms of neurological adverse events and/or CRS (pyrexia, tachycardia, hypotension, chills, hypoxia) should be advised not to drive or use machines until symptoms resolve (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (≥ 20%) were cytokine release syndrome, neutropenia, anaemia and thrombocytopenia and rash.

The most common serious adverse reactions reported in ≥ 2% of patients were cytokine release syndrome (22.1%), sepsis (4.1%), COVID-19 (3.4%), tumour flare (3.4%), COVID-19 pneumonia (2.8%), febrile neutropenia (2.1%), neutropenia (2.1%), and pleural effusion (2.1%).

Permanent discontinuation of glofitamab due to an adverse reaction occurred in 5.5% of patients. The most common adverse reactions leading to permanent discontinuation of glofitamab were COVID-19 (1.4%) and neutropenia (1.4%).

Tabulated list of adverse reactions

Adverse reactions occurring in relapsed or refractory DLBCL patients treated with glofitamab monotherapy (n=145) in study NP30179 are listed in Table 4. Patients received a median of 5 cycles of Glofitamab treatment (range 1:13 cycles).

The adverse reactions are listed by MedDRA system organ class and categories of frequency. The following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4. Adverse reactions reported in patients with relapsed or refractory DLBCL treated with glofitamab monotherapy

System organ class	Adverse reaction	All grades	Grade 3−4
Infections and infestations	Viral infections[1]	Very common	Common*
	Bacterial infections[2]	Common	Common
	Upper respiratory tract infections[3]	Common	Very rare**
	Sepsis[4]	Common	Common*
	Lower respiratory tract infections[5]	Common	Very rare**
	Pneumonia	Common	Uncommon
	Urinary tract infection[6]	Common	Uncommon
	Fungal infections[7]	Common	Very rare**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumour flare	Very common	Common
Blood and lymphatic system disorders	Neutropenia	Very common	Very Common
	Anaemia	Very common	Common
	Thrombocytopenia	Very common	Common
	Lymphopenia	Common	Common
	Febrile neutropenia[8]	Common	Common
Immune system disorders	Cytokine release syndrome[9]	Very common	Common
Metabolism and nutrition disorders	Hypophosphataemia	Very common	Common
	Hypomagnesaemia	Very common	Very rare**
	Hypocalcaemia	Very common	Very rare**
	Hypokalaemia	Very common	Uncommon
	Hyponatraemia	Common	Common
	Tumour lysis syndrome	Common	Common
Psychiatric disorders	Confusional state	Common	Very rare**

Nervous system disorders	Headache	Very common	Very rare**
	Somnolence	Common	Uncommon
	Tremor	Common	Very rare**
	Myelitis[10]	Uncommon	Uncommon
Gastrointestinal disorders	Constipation	Very common	Very rare**
	Diarrhoea	Very common	Very rare**
	Nausea	Very common	Very rare**
	Gastrointestinal haemorrhage[11]	Common	Common
	Vomiting	Common	Very rare**
Skin and subcutaneous tissue disorders	Rash[12]	Very common	Common
General disorders and administration site conditions	Pyrexia	Very common	Very rare**
Investigations	Alanine aminotransferase increased	Common	Common
	Aspartate aminotransferase increased	Common	Common
	Blood alkaline phosphatase increased	Common	Common
	Gamma-glutamyltransferase increased	Common	Common
	Blood bilirubin increased	Common	Uncommon
	Hepatic enzyme increased	Common	Common

* Grade 5 reactions reported. See serious infections in *Description of selected adverse reactions.*

** No Grade 3-4 events were reported.

[1] Includes COVID-19, COVID-19 pneumonia, herpes zoster, influenza, and ophthalmic herpes zoster.

[2] Includes vascular device infection, bacterial infection, Campylobacter infection, biliary tract infection bacterial, urinary tract infection bacterial, *Clostridium difficile* infection, Escherichia infection, and peritonitis.

[3] Includes upper respiratory tract infection, sinusitis, nasopharyngitis, chronic sinusitis, and rhinitis.

[4] Includes sepsis and septic shock.

[5] Includes lower respiratory tract infection and bronchitis.

[6] Includes urinary tract infection and Escherichia urinary tract infection.

[7] Includes oesophageal candidiasis and oral candidiasis.

[8] Includes febrile neutropenia and neutropenic infection.

[9] Based on ASTCT consensus grading (Lee 2019).

[10] Myelitis occurred concurrently with CRS.

[11] Includes gastrointestinal haemorrhage, large intestinal haemorrhage, and gastric haemorrhage.

[12] Includes rash, rash pruritic, rash maculo-papular, dermatitis, dermatitis acneiform, dermatitis exfoliative, erythema, palmar erythema, pruritis, and rash erythematous.

Description of selected adverse reactions

Cytokine release syndrome

In study NP30179, any grade CRS (by ASTCT criteria) occurred in 67.6% of patients, with Grade 1 CRS being reported in 50.3% of patients, Grade 2 CRS in 13.1% patients, Grade 3 CRS in 2.8% of patients and Grade 4 CRS in 1.4% of patients. CRS occurred more than once in 32.4% (47/145) of patients; 36/47 patients experienced multiple Grade 1 CRS events only. There were no fatal cases of CRS. CRS resolved in all patients except one. One patient discontinued treatment due to CRS.

In patients with CRS, the most common manifestations of CRS included pyrexia (99.0%), tachycardia (25.5%),

hypotension (23.5%), chills (14.3%) and hypoxia (12.2%). Grade 3 or higher events associated with CRS included hypotension (3.1%), hypoxia (3.1%), pyrexia (2.0%) and tachycardia (2.0%).

CRS of any grade occurred in 54.5% of patients following the first 2.5 mg dose of glofitamab at Cycle 1 Day 8 with median time to onset (from start of infusion) of 12.6 hours (range: 5.2 to 50.8 hours) and median duration of 31.8 hours (range: 0.5 to 316.7 hours); in 33.3% of patients following the 10 mg dose at Cycle 1 Day 15 with median time to onset of 26.8 hours (range: 6.7 to 125.0 hours) and median duration of 16.5 hours (range: 0.3 to 109.2 hours); and in 26.8% of patients following the 30 mg dose at Cycle 2 with median time to onset of 28.2 hours (range: 15.0 to 44.2 hours) and median duration of 18.9 hours (range: 1.0 to 180.5 hours). CRS was reported in 0.9% of patients at Cycle 3 and in 2% of patients beyond Cycle 3.

Grade ≥ 2 CRS occurred in 12.4% of patients following the first glofitamab dose (2.5 mg) with median time to onset of 9.7 hours (range: 5.2 to 19.1 hours) and median duration of 50.4 hours (range: 6.5 to 316.7 hours). Following glofitamab 10 mg dose at Cycle 1 Day 15, the incidence of Grade ≥ 2 CRS decreased to 5.2% of patients with median time to onset of 26.2 hours (range: 6.7 to 144.2 hours) and median duration of 30.9 hours (range: 3.7 to 227.2 hours). Grade ≥ 2 CRS following glofitamab 30 mg dose at Cycle 2 Day 1 occurred in one patient (0.8%) with time to onset of 15.0 hours and duration of 44.8 hours. No Grade ≥ 2 CRS was reported beyond Cycle 2.

In 145 patients, 7 (4.8%) patients experienced elevated liver function tests (AST and ALT > 3 × ULN and/or total bilirubin > 2 × ULN) reported concurrently with CRS (n=6) or with disease progression (n=1).

Among the 25 patients who experienced Grade ≥ 2 CRS after glofitamab, 22 (88.0%) received tocilizumab, 15 (60.0%) received corticosteroids and 14 (56.0%) received both tocilizumab and corticosteroids. Ten patients (40.0%) received oxygen. All 6 patients (24.0%) with Grade 3 or 4 CRS received a single vasopressor.

Hospitalisations due to patients experiencing CRS following glofitamab administration occurred in 22.1% of patients and the reported median duration of hospitalisation was 4 days (range: 2 to 15 days).

Serious infections

In study NP30179, serious infections were reported in 15.9% of patients. The most frequent serious infections reported in ≥ 2% of patients were sepsis (4.1%), COVID-19 (3.4%), and COVID-19 pneumonia (2.8%). Infection-related deaths were reported in 4.8% of patients (due to sepsis, COVID-19 pneumonia and COVID-19). Four patients (2.8%) experienced serious infections concurrently with Grade 3 or 4 neutropenia.

Neutropenia

Neutropenia (including neutrophil count decreased) was reported in 40.0% of patients and severe neutropenia (Grade 3 or 4) was reported in 29.0% of patients. The median time to onset of the first neutropenia event was 29 days (range: 1 to 203 days). Prolonged neutropenia (lasting longer than 30 days) occurred in 11.7% of patients. The majority of patients with neutropenia (79.3%) were treated with G-CSF. Febrile neutropenia was reported in 3.4% of patients.

Tumour flare

Tumour flare was reported in 11.7% of patients, including Grade 2 tumour flare in 4.8% of patients and Grade 3 tumour flare in 2.8% of patients. Tumour flare was reported involving lymph nodes in the head and neck presenting with pain and involving lymph nodes in the thorax with symptoms of breathlessness due to development of pleural effusion. Most tumour flare events (16/17) occurred during Cycle 1, and no tumour flare events were reported beyond Cycle 2. The median time to onset of tumour flare of any grade was 2 days (range: 1 to 16 days), and the median duration was 3.5 days (range: 1 to 35 days).

Among the 11 patients who experienced Grade ≥ 2 tumour flare, 2 (18.2%) patients received analgesics, 6 (54.5%) patients received corticosteroids and analgesics including morphine derivatives, 1 (0.9%) patient received corticosteroids and anti-emetics, and 2 (18.2%) patients did not require treatment. All tumour flare events resolved except in one patient with a Grade ≥ 2 event. No patients discontinued treatment due to tumour

flare.

Tumour lysis syndrome

TLS was reported in 2 patients (1.4%) and was Grade 3 in severity in both cases. The median time to onset of TLS onset was 2 days, and the median duration was 4 days (range: 3 to 5 days).

Reporting of suspected adverse reactions

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554. As glofitamab is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

4.9 Overdose

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX28

Mechanism of action

Glofitamab is a bispecific monoclonal antibody that binds bivalently to CD20 expressed on the surface of B cells and monovalently to CD3 in the T-cell receptor complex expressed on the surface of T cells. By simultaneous binding to CD20 on the B cell and CD3 on the T cell, glofitamab mediates the formation of an immunological synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that results in the lysis of CD20-expressing B cells.

Pharmacodynamics

In Study NP30179, 84% (84/100) patients were already B cell depleted (< 70 cells/µL) before pre-treatment with obinutuzumab. B cell depletion increased to 100% (94/94) after obinutuzumab pre-treatment prior to glofitamab treatment initiation and remained low during glofitamab treatment.

During Cycle 1 (step-up dosing), transient increases in plasma IL-6 levels were observed at 6 hours post glofitamab infusion, which remained elevated at 20 hours post-infusion and returned to baseline prior to the next infusion.

Cardiac electrophysiology
In Study NP30179, 16/145 patients who were exposed to glofitamab experienced a post-baseline QTc value > 450ms. One of these cases was assessed to be of clinical significance by the investigator. No patients discontinued treatment due to QTc prolongation.

Clinical efficacy and safety

Relapsed or refractory DLBCL

An open-label multicenter, multi-cohort trial (NP30179) was conducted to evaluate glofitamab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. In the single-arm monotherapy DLBCL cohort (n=108), patients with relapsed or refractory DLBCL were required to have received at least two prior lines of

systemic therapy, including an anti-CD20 monoclonal antibody and an anthracycline agent. Patients with FL3b and Richter transformation were not eligible. Patients were expected to present CD20-positive DLBCL, but biomarker eligibility was not a requirement for inclusion.

The study excluded patients with ECOG performance status ≥ 2, significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina), significant active pulmonary disease, impaired renal functions (CrCL < 50 mL/min with elevated serum creatinine level), active autoimmune disease requiring immunosuppressive therapy, active infections (i.e., chronic active EBV, acute or chronic hepatitis C, hepatitis B, HIV), progressive multifocal leukoencephalopathy, current or a history of CNS lymphoma or CNS disease, a history of macrophage activation syndrome / hemophagocytic lymphohistiocytosis, prior allogeneic stem cell transplant, prior organ transplantation, or hepatic transaminases ≥ 3 × ULN.

All patients received pre-treatment with obinutuzumab at Cycle 1 Day 1. Patients received 2.5 mg of glofitamab at Cycle 1 Day 8, 10 mg of glofitamab at Cycle 1 Day 15, and 30 mg of glofitamab at Cycle 2 Day 1 as per the step-up dosing schedule. Patients continued to receive 30 mg of glofitamab on Day 1 of Cycles 3 to 12. The duration of each cycle was 21 days. Patients received a median of 5 cycles of glofitamab treatment (range: 1 to 13 cycles) with 34.7% receiving 8 or more cycles and 25.7% receiving 12 cycles of glofitamab treatment.

The baseline demographic and disease characteristics were: median age 66 years (range: 21 to 90 years) with 53.7% being 65 years or older and 15.7% being 75 years or older; 69.4% males; 74.1% white, 5.6% Asian and 0.9% Black or African American; 5.6% Hispanic or Latino; and ECOG performance status of 0 (46.3%) or 1 (52.8%). Most patients (71.3%) had DLBCL not otherwise specified, 7.4% had DLBCL transformed from follicular lymphoma, 8.3% had high grade B-cell lymphoma (HGBCL) or another histology transformed from follicular lymphoma, 7.4% had HGBCL, and 5.6% had primary mediastinal B-cell lymphoma (PMBCL). The median number of prior lines of therapy was 3 (range: 2 to 7), with 39.8% of patients having received 2 prior lines and 60.2% having received 3 or more prior lines of therapy. All patients had received prior chemotherapy (all patients received alkylator therapy and 98.1% of patients received anthracycline therapy) and all patients had received prior anti-CD20 monoclonal antibody therapy; 35.2% of patients had received prior CAR T-cell therapy, and 16.7% of patients had received autologous stem cell transplant. Most patients (89.8%) had refractory disease, 60.2% of patients had primary refractory disease and 83.3% of patients were refractory to their last prior therapy.

The primary efficacy outcome measure was complete response (CR) rate as assessed by an independent review committee (IRC) using 2014 Lugano criteria. The overall median duration of follow-up was 15 months (range: 0 to 21 months). The secondary efficacy outcome measures included overall response rate (ORR), duration of response (DOR), duration of complete response (DOCR), and time to first complete response (TFCR) as assessed by IRC
Efficacy results are summarized in Table 5.

Table 5. Summary of efficacy in patients with relapsed or refractory DLBCL

Efficacy endpoints	glofitamab N=108
Complete response	
Patients with CR, n (%)	38 (35.2)
95% CI	[26.24, 44.96]
Overall response rate	
Patients with CR or PR, n (%)	54 (50.0)
95% CI	[40.22, 59.78]
Duration of complete response[1]	
Median DOCR, months [95% CI]	NE [18.4, NE]
Range, months	0[2]–20[2]
12-month DOCR, % [95% CI][3]	74.6 [59.19, 89.93]

Duration of response[4]	
Median duration, months [95% CI]	14.4 [8.6, NE]
Range, months	0[2]–20[2]
Time to first complete response	
Median TFCR, days [95% CI]	42 [41, 47]
Range, days	31–308

CI=confidence interval; NE=not estimable; PR=partial response.
Hypothesis testing was conducted on the primary endpoint of IRC-assessed CR rate.
[1] DOCR is defined as the date of first complete response until disease progression or death due to any cause.
[2] Censored observations.
[3] Event-free rates based on Kaplan-Meier estimates.
[4] DOR is defined as the date of first response (PR or CR) until disease progression or death due to any cause.

The median follow-up for DOR was 12.8 months (range: 0 to 20 months).

Immunogenicity

Of 418 patients in study NP30179, only two (0.5%) patients were negative for anti-glofitamab antibodies at baseline and became positive following treatment. Due to the limited number of patients with antibodies against glofitamab, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with glofitamab in one or more subsets of the paediatric population in treatment of mature B-cell neoplasms (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Non-compartmental analyses indicate that glofitamab serum concentration reaches the maximal level (C_{max}) at the end of infusion and declines in a bi-exponential fashion. Glofitamab exhibits linear and dose-proportional pharmacokinetics over the dose range studied (0.005 to 30 mg) and is independent of time.

Absorption

Glofitamab is administered as an intravenous infusion. Peak concentration of glofitamab (C_{max}) was reached at the end of the infusion.

Distribution

Following intravenous administration, the central volume of distribution was 3.33 L, which is close to total serum volume. The peripheral volume of distribution was 2.18 L.

Biotransformation

The metabolism of glofitamab has not been studied. Antibodies are cleared principally by catabolism.

Elimination

The glofitamab serum concentration-time data are described by a population pharmacokinetic model with two compartments, and both time-independent clearance and time-varying clearance.

The time-independent clearance pathway was estimated as 0.602 L/day and the initial time-varying clearance pathway as 0.396 L/day, with an exponential decay over time (K_{des} ~ 0.445/day). The estimated decay half-life from the initial total clearance value to the time-independent clearance only was estimated as 1.56 days.

The effective half-life in the linear phase (i.e., after the contribution of time-varying clearance has collapsed to a negligible amount) can be approximated to a typical linear effective half-life of 6.54 days (95% CI: 3.74 - 9.41) based on the population pharmacokinetic analysis.

Special populations

Elderly
No differences in glofitamab exposure were noted in patients 65 years of age and older and those under 65 years based on population pharmacokinetic analysis.

Renal impairment
The population pharmacokinetic analysis of glofitamab showed that creatinine clearance does not affect the pharmacokinetics of glofitamab. The pharmacokinetics of glofitamab in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min) were similar to those in patients with normal renal function. glofitamab has not been studied in patients with severe renal impairment.

Hepatic impairment
Population pharmacokinetic analyses showed mild hepatic impairment does not affect the pharmacokinetics of glofitamab. The pharmacokinetics of glofitamab in patients with mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 × ULN or AST > ULN) were similar to those with normal hepatic functions. glofitamab has not been studied in patients with moderate or severe hepatic impairment.

Effects of age, gender and body weight
No clinically significant differences in the pharmacokinetics of glofitamab were observed based on age (21 years to 90 years), gender and body weight (31 kg to 148 kg).

5.3 Preclinical safety data

No studies have been conducted to establish the carcinogenic potential and mutagenic potential of glofitamab.

Fertility

No fertility assessments in animals have been performed to evaluate the effect of glofitamab.

Reproductive Toxicity

No reproductive and developmental toxicity studies in animals have been performed to evaluate the effect of glofitamab. Based on low placental transfer of antibodies during the first trimester, the mechanism of action of glofitamab (B-cell depletion, target-dependent T-cell activation, and cytokine release), the available safety data with glofitamab and data on other anti-CD20 antibodies, the risk for teratogenicity is low. Prolonged B-cell depletion can lead to increased risk of opportunistic infection, which may cause foetal loss. Transient CRS associated with glofitamab administration may also be harmful to the foetus (see section 4.6).

Systemic Toxicity
In a study in cynomolgus monkeys, animals experiencing severe CRS after a single intravenous dose of glofitamab (0.1 mg/kg) without obinutuzumab pre-treatment had erosions in the gastrointestinal tract and inflammatory cell infiltrates in spleen and sinusoids of the liver and sporadically in some other organs. These inflammatory cell infiltrates were likely secondary to cytokine-induced immune cell activation. Pre-treatment with obinutuzumab resulted in the attenuation of glofitamab-induced cytokine release and related adverse effects by depleting B cells in peripheral blood and lymphoid tissue. This allowed at least 10 times higher doses of glofitamab (1 mg/kg) in cynomolgus monkeys resulting in a C_{max} of up to 3.74 times the human C_{max} at the recommended 30 mg dose.

All findings with glofitamab were considered pharmacologically mediated effects and reversible. Studies longer than 4 weeks were not performed, as glofitamab was highly immunogenic in cynomolgus monkeys and led to

loss of exposure and loss of the pharmacologic effect.

As all relapsed or refractory DLBCL patients to be treated have been exposed to anti-CD20 treatment before, the majority will likely have low circulating B cell levels due to residual effects of prior anti-CD20 therapy, before treatment with obinutuzumab. Therefore, the animal model without prior rituximab (or other anti-CD20) treatment may not fully reflect the clinical context.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
L-methionine
Sucrose
Polysorbate 20 (E432)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years

Diluted solution for intravenous infusion

Chemical and physical in-use stability have been demonstrated for a maximum of 72 hours at 2 °C to 8 °C and 24 hours at 30 °C followed by a maximum infusion time of 8 hours.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL concentrate in a 15 mL vial (colourless Type I glass) with stopper (butyl rubber).
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for dilution

- Glofitamab contains no preservative and is intended for single use only
- Glofitamab must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration.
- Visually inspect the glofitamab vial for particulate matter or discoloration prior to administration. Glofitamab is a colorless, clear solution. Discard the vial if the solution is cloudy, discolored or contains visible particles.
- Withdraw the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or sodium chloride 4.5 mg/mL (0.45%) solution for injection, as described in Table 6, from the infusion bag using a sterile needle and syringe and discard.
- Withdraw the required volume of glofitamab concentrate for the intended dose from the vial using a sterile needle and syringe and dilute into the infusion bag (see Table 6). Discard any unused portion left in the vial.
- The final glofitamab concentration after dilution must be 0.1 mg/mL to 0.6 mg/mL.
- Gently invert the infusion bag to mix the solution in order to avoid excessive foaming. Do not shake.
- Inspect the infusion bag for particulates and discard if present.
  - Prior to the start of the intravenous infusion, the content of the infusion bag should be at room temperature (25°C).

Table 6. Dilution of glofitamab for infusion

Dose of glofitamab to be administered	Size of infusion bag	Volume of sodium chloride 9mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection to be withdrawn and discarded	Volume of glofitamab concentrate to be added
2.5 mg	50 mL	27.5 mL	2.5 mL
	100 mL	77.5 mL	2.5 mL
10 mg	50 mL	10 mL	10 mL
	100 mL	10 mL	10 mL
30 mg	50 mL	30 mL	30 mL
	100 mL	30 mL	30 mL

Only sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection should be used to dilute glofitamab, since other solvents have not been tested.

When diluted with sodium chloride 9 mg/mL (0.9%) solution is compatible with intravenous infusion bags composed of polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP) or non-PVC polyolefin. When diluted with sodium chloride 4.5 mg/mL (0.45%) solution, glofitamab is compatible with intravenous infusion bags composed of PVC.

No incompatibilities have been observed with infusion sets with product-contacting surfaces of polyurethane (PUR), PVC or PE, and in-line filter membranes composed of polyethersulfone (PES) or polysulfone. The use of in-line filter membranes is optional.

Disposal

Glofitamab vial is for single use only.

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

7. SCIENTIFIC OPINION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. EAMS NUMBER

EAMS number [00031/0018]

9. DATE OF SCIENTIFIC OPINION
30/06/2023

Additional information

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm patient eligibility for the scheme, once the patient has signed the informed consent form. These forms can be requested by sending an email to welwyn.glofitamabEAMS@roche.com. An agreement, outlining the treating physician's responsibilities and safety obligations, will be signed by the prescribing physician. Once the signed documents are returned, Roche will arrange safety training and each prescribing haematologist will also be provided with a physician pack containing all the relevant documents needed, including the adverse events reporting form needed to manage patients receiving glofitamab under the EAMS.

Contact information

Contact details for reporting Adverse Events/Special Situations/Pregnancies:

SAE Email Address: welwyn.uk_dsc@roche.com

SAE Facsimile Transmission: +44 1707 367582

SAE TELEPHONE CONTACT: +44 1707 367554

Name: UK Drug Safety Centre

Contact email for the EAMS programme (excluding AE reporting):

welwyn.glofitamabEAMS@roche.com

Contact Details for Medical Information

Roche Medical Information on 0800 328 1629 or email medinfo.uk@roche.com