ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Columvi 2.5 mg concentrate for solution for infusion
Columvi 10 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Columvi 2.5 mg concentrate for solution for infusion

Each vial of 2.5 mL of concentrate contains 2.5 mg of glofitamab at a concentration of 1 mg/mL.

Columvi 10 mg concentrate for solution for infusion

Each vial of 10 mL of concentrate contains 10 mg of glofitamab at a concentration of 1 mg/mL.

Glofitamab is a humanised 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 Therapeutic indications

Columvi 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

Columvi 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 Columvi 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 Columvi treatment) to lower the circulating and lymphoid B cells (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 prophylaxis

Cytokine release syndrome prophylaxis
Columvi should be administered to well-hydrated patients. Recommended premedication for CRS (see section 4.4) is outlined in Table 1.

Table 1. Premedication before Columvi infusion

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 Columvi infusion
		Oral analgesic / anti-pyretic[2]	At least 30 minutes before Columvi infusion
		Anti-histamine[3]	
All subsequent infusions	All patients	Oral analgesic / anti-pyretic[2]	At least 30 minutes before Columvi infusion
		Anti-histamine[3]	
	Patients who experienced CRS with the previous dose	Intravenous glucocorticoid[1, 4]	Completed at least 1 hour prior to Columvi 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

Columvi 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.

Columvi dose step-up schedule
Columvi 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. Columvi monotherapy dose step-up schedule for patients with relapsed or refractory DLBCL

Treatment cycle, Day		Dose of Columvi	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 Columvi, 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 10 hours after completion of the infusion of the first Columvi dose (2.5 mg on Cycle 1 Day 8) (see section 4.8).

- Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of the infusion (see Table 3 in section 4.2).

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 Columvi is recommended for a maximum of 12 cycles or until disease progression or unmanageable toxicity. Each cycle is 21 days.

Delayed or missed doses
During step-up dosing (weekly dosing):

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

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

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

After Cycle 2 (30 mg dose):

- If there is a Columvi treatment-free interval of more than 6 weeks between cycles, then repeat pre-treatment with obinutuzumab and Columvi 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 Columvi are recommended.

Management of cytokine release syndrome
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 Columvi infusion**
Grade 1 Fever ≥ 38 °C	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Restart infusion at slower rate when symptoms resolve • 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]	• Ensure symptoms are resolved for at least 72 hours prior to next infusion • Consider slower infusion rate[2]
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		

<table>
<tr><th>Grade[1]</th><th>CRS management</th><th>For next scheduled Columvi infusion</th></tr>
<tr><td>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</td><td>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]</td><td>• 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 Columvi</td></tr>
<tr><td>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)</td><td colspan="2">If CRS occurs during infusion or post-infusion:
• Permanently discontinue Columvi and treat symptoms
• Administer corticosteroids[3]
• Administer tocilizumab[4]</td></tr>
<tr><td colspan="3">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</td></tr>
</table>

[1] ASTCT consensus grading criteria (Lee 2019).

[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), as administered in Study NP30179.

[5] In Study NP30179, Grade ≥ 2 CRS following Columvi 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 Columvi 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). Columvi 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). Columvi has not been studied in patients with severe renal impairment (see section 5.2).

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

Method of administration

Columvi is for intravenous use only.

Columvi 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.

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

For instructions on dilution of Columvi 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.

CD20-negative disease

There are limited data available on patients with CD20-negative DLBCL treated with Columvi and it is possible that patients with CD20-negative DLBCL may have less benefit compared to patients with CD20-positive DLBCL. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL with Columvi should be considered.

Cytokine release syndrome

CRS, including life-threatening reactions, has been reported in patients receiving Columvi (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 Columvi. Elevated liver function tests (AST and alanine transaminase [ALT] > 3 × ULN and/or total bilirubin > 2 × ULN) concurrent with CRS have been reported after Columvi use (see section 4.8).

Patients in study NP30179 were pre-treated with obinutuzumab, 7 days prior to initiation of Columvi 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 Columvi 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 Columvi infusions and for at least 10 hours after completion of the first infusion. 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 (section 4.2).

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.

Interaction with CYP450 substrates

The initial release of cytokines associated with the start of Columvi treatment could suppress CYP450 enzymes and lead to fluctuations in concentrations of concomitantly administered drugs. On initiation of Columvi 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 (see section 4.5).

Serious infections

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

Columvi must not be administered to patients with an active infection. Caution should be exercised when considering the use of Columvi 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 Columvi treatment for the emergence of possible bacterial, fungal, and new or reactivated viral infections and treated appropriately.

Columvi 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 Columvi. Patients with febrile neutropenia should be evaluated for infection and treated promptly.

Tumour flare

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

Consistent with the mechanism of action of Columvi, tumour flare is likely due to the influx of T cells into tumour sites following Columvi 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 Columvi 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 Columvi (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 Columvi 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 Columvi therapy has not been studied. Immunisation with live vaccines is not recommended during Columvi therapy.

4.5 Interaction with other medicinal products and other forms of interaction

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

The initial release of cytokines associated with the start of Columvi 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 Columvi (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 Columvi therapy, patients being treated with CYP450 substrates with a narrow therapeutic index should be monitored.

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 Columvi and for at least 2 months following the last dose of Columvi.

Pregnancy

There are no data on the use of Columvi 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.

Columvi is not recommended during pregnancy and in women of childbearing potential not using contraception. Female patients receiving Columvi 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 breast-feeding child is unknown. Women should be advised to discontinue breast-feeding during treatment with Columvi and for 2 months after the final dose of Columvi.

Fertility

No human data on fertility are available. 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

Columvi 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, 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 Columvi due to an adverse reaction occurred in 5.5% of patients. The most common adverse reactions leading to permanent discontinuation of Columvi 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 Columvi monotherapy (n=145) in study NP30179 are listed in Table 4. Patients received a median of 5 cycles of Columvi treatment (range: 1 to 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 Columvi 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**

System organ class	Adverse reaction	All grades	Grade 3–4
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 Columvi 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 Columvi 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 Columvi 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 Columvi 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 Columvi, 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 Columvi 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 (9.1%) 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose in clinical trials. 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 Columvi treatment initiation and remained low during Columvi treatment.

During Cycle 1 (step-up dosing), transient increases in plasma IL-6 levels were observed at 6 hours post Columvi 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 Columvi 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 (see section 4.4).

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 Columvi at Cycle 1 Day 8, 10 mg of Columvi at Cycle 1 Day 15, and 30 mg of Columvi at Cycle 2 Day 1 as per the step-up dosing schedule. Patients continued to receive 30 mg of Columvi on Day 1 of Cycles 3 to 12. The duration of each cycle was 21 days. Patients received a median of 5 cycles of Columvi treatment (range: 1 to 13 cycles) with 34.7% receiving 8 or more cycles and 25.7% receiving 12 cycles of Columvi 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	**Columvi 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 European Medicines Agency has deferred the obligation to submit the results of studies with Columvi 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).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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

Columvi 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) is 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. Columvi 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. Columvi 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 Columvi 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

30 months.

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 - 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

Columvi 2.5 mg concentrate for solution for infusion

2.5 mL concentrate for solution for infusion in a 6 mL vial (colourless Type I glass) with stopper (butyl rubber).
Pack size of 1 vial.

Columvi 10 mg concentrate for solution for infusion

10 mL concentrate for solution for infusion 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

- Columvi contains no preservative and is intended for single use only.
- Columvi must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration.
- Visually inspect the Columvi vial for particulate matter or discoloration prior to administration. Columvi 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 Columvi 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 Columvi for infusion

Dose of Columvi to be administered	Size of infusion bag	Volume of sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection to be withdrawn and discarded	Volume of Columvi 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 Columvi, since other solvents have not been tested.

When diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, Columvi 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 for injection, Columvi 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

Columvi vial is for single use only.

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1742/001
EU/1/23/1742/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 July 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Roche Diagnostics GmbH
Nonnenwald 2
82377 Penzberg
Germany

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of Columvi in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at:
- Informing physicians to provide each patient with the patient card and educate the patient on its content, which includes a list of symptoms of CRS to prompt patient actions including to seek immediate medical attention in case of its occurrence.
- Prompting patient actions, including seeking immediate medical attention, in case of the occurrence of symptoms of CRS.
- Informing physicians on the risk of tumour flare and its manifestations.

The MAH shall ensure that in each Member State where Columvi is marketed, all healthcare professionals (HCPs) who are expected to prescribe, dispense, or use Columvi have access to/are provided with a healthcare professional brochure, which will contain:
- A description of tumour flare, and information on early recognition, appropriate diagnosis, and monitoring of tumour flare.
- A reminder to provide each patient with the patient card, which includes a list of symptoms of CRS to prompt patients to seek immediate medical attention in case of their occurrence.

All patients who receive Columvi shall be provided with a patient card, which will contain the following key elements:
- Contact details of the Columvi prescriber.
- List of CRS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence.
- Instructions that the patient should carry the patient card at all times and to share it with HCPs involved in their care (i.e., urgent care HCPs, etc.).
- Information for the HCPs treating the patient that Columvi treatment is associated with the risk of CRS.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH shall provide the updated clinical study report with a minimum of 2 years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179 in scope of procedure EMEA/H/C/005751/0000.	Q4 2024
In order to provide further evidence of efficacy and safety of glofitamab in DLBCL, the MAH will provide the results of Study GO41944, a phase III open-label, multicentre, randomised study evaluating the efficacy and safety of glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed or refractory DLBCL.	Q3 2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Columvi 2.5 mg concentrate for solution for infusion
glofitamab

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial of 2.5 mL contains 2.5 mg glofitamab at a concentration of 1 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
2.5 mg/2.5 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous use after dilution
For single use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1742/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Columvi 2.5 mg sterile concentrate for solution for infusion
glofitamab
Intravenous use

2. METHOD OF ADMINISTRATION

IV after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mg/2.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Columvi 10 mg concentrate for solution for infusion
glofitamab

2. STATEMENT OF ACTIVE SUBSTANCE

1 vial of 10 mL contains 10 mg glofitamab at a concentration of 1 mg/mL.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, sucrose, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
10 mg/ 10 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous use after dilution
For single use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1742/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Columvi 10 mg sterile concentrate for solution for infusion
glofitamab
Intravenous use

2. METHOD OF ADMINISTRATION

IV after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg/10 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Columvi 2.5 mg concentrate for solution for infusion
Columvi 10 mg concentrate for solution for infusion
glofitamab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
  - Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it. Keep this Patient Card with you at all times.
  - Always show the Patient Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Columvi is and what it is used for

What Columvi is

Columvi is a cancer medicine that contains the active substance glofitamab.

What Columvi is used for

Columvi is used to treat adults with a cancer called “diffuse large B-cell lymphoma” (DLBCL). It is used when the cancer:
- has come back (relapsed), or
- did not respond to previous treatments.

Diffuse large B-cell lymphoma is a cancer of a part of your immune system (the body’s defences).
- It affects a type of white blood cell called ‘B cells’.
- In DLBCL, B cells multiply in an uncontrolled manner and build up in your tissues.

How Columvi works

- The active substance in Columvi, glofitamab, is a bispecific monoclonal antibody, a type of protein that attaches to two specific targets in the body. It attaches to a specific protein on the surface of B cells, including cancerous B cells, and also to another protein on the surface of T cells (another type of white blood cell). This activates T cells and causes them to multiply. This, in turn, results in the destruction of the B cells, including the cancerous cells.

2. What you need to know before you are given Columvi

You must not be given Columvi

- if you are allergic to glofitamab or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to obinutuzumab, which is another medicine given before starting Columvi treatment (see also section 3 'How Columvi is given'), or any of the other ingredients of this medicine

If you are not sure if any of the above apply to you, talk to your doctor or nurse before you are given Columvi.

Warnings and precautions

Talk to your doctor before you are given Columvi if
- you have an infection
- you have had a long-lasting infection (chronic), or an infection which keeps coming back (recurring)
- you have or had any kidney, liver or heart problems
- you are planning to have a vaccine in the near future

If any of the above apply to you (or you are not sure), talk to your doctor before being given Columvi.

Pay attention to serious side effects.

Some side effects of Columvi are serious and can be life-threatening. These may happen any time during Columvi treatment.

Tell your doctor straight away if you experience any of the following side effects while receiving Columvi. The symptoms of each side effect are listed in section 4.

- **Cytokine release syndrome:** an exaggerated inflammatory condition associated with medicines that stimulate T cells, characterized by fever and impairment to multiple organs in the body. Cytokine release syndrome is more likely to occur during Cycle 1 after Columvi is given (see section 3 'How Columvi is given'). Close monitoring is needed. Before each infusion, you may be given medicines, which help reduce possible side effects of cytokine release syndrome.
- **Tumour lysis syndrome:** some people may get unusual levels of some salts in the blood (such as potassium and uric acid) – caused by the fast breakdown of cancer cells during treatment. Your doctor or nurse will do blood tests to check for this condition. Before each infusion, you should be well-hydrated and may be given medicines that can help reduce high levels of uric acid. These may help reduce possible side effects of tumour lysis syndrome.
- **Tumour flare:** a reaction to certain medicines that act on the immune system which is/appears similar to worsening of the cancer.
- **Infections:** you may get signs of infection, which can vary depending on where in the body the infection is.

If you have, or think you may have, any of the above symptoms tell your doctor straight away.
Your doctor may:
- give you other medicines to reduce symptoms and prevent complications,
- stop your treatment for a short time, or
- stop your treatment completely.

Children and adolescents

This medicine should not be given to children and adolescents below 18 years of age. This is because Columvi has not been studied in this age group.

Other medicines and Columvi

Tell your doctor or nurse if you are taking, have recently taken or might start taking any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy and contraception

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- You should not be given Columvi if you are pregnant. This is because it is possible that Columvi could harm your unborn baby.
- If you could become pregnant, you must use effective contraception while you are being treated with Columvi and for 2 months after the last dose.
- If you become pregnant while you are being treated with Columvi tell your doctor immediately.

Breast-feeding

Do not breast-feed while receiving Columvi and for at least 2 months after the last dose. This is because it is not known if this medicine can pass into breast milk and harm your baby.

Driving and using machines

Columvi has minor influence on your ability to drive, cycle or use any tools or machines.

If you feel any symptoms that may affect your ability to drive, including symptoms of cytokine release syndrome (such as fever, fast heartbeat, feeling dizzy or lightheaded, chills or shortness of breath) – do not drive, cycle or use any tools or machines until you feel better. See section 4 for more information about side effects.

3. How Columvi is given

You will be given Columvi under the supervision of a doctor experienced in cancer treatment, in a hospital or clinic.

Medicines given before Columvi treatment

- **Seven days before starting Columvi treatment**, you will be given another medicine, obinutuzumab, to reduce the number of B cells in your blood.
- **30 to 60 minutes before you are given Columvi**, you may be given other medicines (pre-medication) to help reduce reactions associated with cytokine release syndrome. These medicines may include:
  - A corticosteroid such as dexamethasone
  - A fever-reducing medicine such as paracetamol
  - An antihistamine such as diphenhydramine

How much and how often you will receive Columvi

You may be given up to 12 treatment cycles of Columvi. Each cycle lasts 21 days. During the first two cycles, your doctor will begin Columvi treatment with a low dose and will gradually increase it to the full dose.

A typical schedule is shown below.

Cycle 1: This will include a pre-treatment and 2 low doses of Columvi during the 21 days:
- Day 1 – Pre-treatment with obinutuzumab

- Day 8 – 2.5 mg starting dose of Columvi
- Day 15 – 10 mg intermediate dose of Columvi

Cycle 2 to Cycle 12: This will be just one dose in the 21 days:
- Day 1 – 30 mg full dose of Columvi

How Columvi is given and monitoring

Columvi is given as a drip into a vein (an intravenous infusion). Your doctor will adjust the time required for infusion depending on how you respond to treatment.
- Your first infusion will be given over 4 hours. Your doctor will monitor you carefully during the first infusion and for 10 hours after completion of infusion. This is to watch for any signs or symptoms of cytokine release syndrome.
- For following infusions, your doctor may require to monitor you after completion of infusion. This will be necessary if you have had moderate or severe cytokine release syndrome with your previous dose.
- If you do not have any cytokine release syndrome after 3 doses, your doctor may give the following infusions over 2 hours.

If you miss a dose of Columvi

If you miss an appointment, make another one straight away. For the treatment to be fully effective, it is very important not to miss a dose.

Before stopping Columvi treatment

Speak with your doctor before stopping treatment. This is because stopping treatment may make your condition worse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

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

Serious side effects

Tell your doctor straight away if you get any of the serious side effects listed below – you may need urgent medical treatment.

- **Cytokine release syndrome (very common):** symptoms may include, but are not limited to, fever, fast heartbeat, feeling dizzy or lightheaded, nausea, headache, rash, confusion, chills, shortness of breath
- **Infections (very common):** symptoms may include, but are not limited to, fever, chills, difficulty breathing, burning pain when passing urine
- **Tumour flare (very common):** symptoms may include, but are not limited to, tender swollen lymph nodes, chest pain, inability to breathe easily, pain at the site of the tumour
- **Tumour lysis syndrome (common):** symptoms may include, but are not limited to, weakness, shortness of breath, feeling confused, irregular heartbeat, muscle cramps

Other side effects

Tell your doctor or nurse straight away if you notice any of the following side effects or if they get worse:

Very common (may affect more than 1 in 10 people)

- lowered levels, as measured in blood tests, of:
  - neutrophils (a type of white blood cell; neutropenia), which may cause fever or any symptoms of an infection
  - red blood cells (anaemia), which may cause tiredness, feeling unwell and pale skin
  - platelets (a type of blood cell; thrombocytopenia), which may cause bruising or bleeding
- fever
- low levels, as measured in blood tests, of phosphate, magnesium, calcium or potassium
- rash
- constipation
- diarrhoea
- feeling sick (nausea)
- viral infections, such as lung infection, shingles
- headache

Common (may affect up to 1 in 10 people)

- low sodium levels, as measured in blood tests, which may cause tiredness, muscle twitching or cramps
- increased levels, as measured in blood tests, of liver enzymes and bilirubin (yellow substance in blood), which may cause yellowing of skin or eyes, and dark urine
- bacterial infections, such as urinary tract infection, infection in or around the stomach
- fungal infection
- nose and throat infections (upper respiratory tract infections)
- infections of the lungs such as bronchitis or pneumonia (lower respiratory tract infections), which may cause fever, cough, and difficulty breathing
- blood poisoning (sepsis), which may cause fever, chills and confusion
- low levels, as measured in blood tests, of lymphocytes (a type of white blood cell; lymphopenia)
- fever with low levels of neutrophils (febrile neutropenia)
- vomiting
- bleeding in the stomach or gut (gastrointestinal haemorrhage), which may cause black stools or blood in vomit
- confusion
- trembling
- sleepiness

Uncommon (may affect less than 1 in 100 people)

- swelling of the spinal cord (myelitis), which may cause muscle weakness or numbness

If you notice any of the side effects above or if they get worse, tell your doctor straight away.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Columvi

Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not use this medicine if it appears cloudy, discoloured or contains particles.

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

6. Contents of the pack and other information

What Columvi contains

- The active substance is glofitamab.
- Columvi 2.5 mg: Each vial contains 2.5 milligrams of glofitamab (in 2.5 mL concentrate) at a concentration of 1 mg/mL
- Columvi 10 mg: Each vial contains 10 milligrams of glofitamab (in 10 mL concentrate) at a concentration of 1 mg/mL
- The other ingredients are: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, sucrose, polysorbate 20 (E432) and water for injections.

What Columvi looks like and contents of the pack

Columvi concentrate for solution for infusion (sterile concentrate) is a colourless, clear solution provided in a glass vial.

Each pack of Columvi contains one vial.

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Columvi must be administered as an intravenous infusion through a dedicated infusion line. It must not be administered as an intravenous push or bolus.

For instructions on dilution of Columvi before administration, see below.

Instructions for dilution

- Columvi contains no preservative and is intended for single use only
- Columvi must be diluted by a healthcare professional using aseptic technique, prior to intravenous administration.
- Do not shake the vial. Visually inspect the Columvi vial for particulate matter or discoloration prior to administration. Columvi 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 1, from the infusion bag using a sterile needle and syringe and discard.
- Withdraw the required volume of Columvi concentrate for the intended dose from the vial using a sterile needle and syringe and dilute into the infusion bag (see Table 1 below). 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 1. Dilution of Columvi for infusion

Dose of Columvi to be administered	**Size of infusion bag**	**Volume of sodium chloride 9 mg/mL (0.9%) or 4.5 mg/mL (0.45%) solution for injection to be withdrawn and discarded**	**Volume of Columvi 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 Columvi, since other solvents have not been tested.

When diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, Columvi 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 for injection, Columvi 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.

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.

Disposal

Columvi vial is for single use only.

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