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

Tepkinly 4 mg/0.8 ml concentrate for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.8 ml vial contains 4 mg of epcoritamab at a concentration of 5 mg/ml.

Each vial contains an overfill that allows withdrawal of the labelled amount.

Epcoritamab is a humanised immunoglobulin G1 (IgG1)-bispecific antibody against CD3 and CD20 antigens, produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipient with known effect
Each vial of Tepkinly contains 21.9 mg of sorbitol. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection (sterile concentrate)

Colourless to slightly yellow solution, pH 5.5 and osmolality of approximately 211 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tepkinly 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

Tepkinly must only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapy. At least 1 dose of tocilizumab for use in the event of CRS should be available prior to epcoritamab administration for Cycle 1. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose should be available.

Posology

Recommended pre-medication and dose schedule

Tepkinly should be administered according to the following dosing schedule in 28-day cycles which is outlined in Table 1.

Table 1 Dosing schedule

Dosing schedule	Cycle of treatment	Days	Epcoritamab dose (mg)[a]
Weekly	Cycle 1	1	0.16 mg (Step-up dose 1)
		8	0.8 mg (Step-up dose 2)
		15	48 mg (First full dose)
		22	48 mg
Weekly	Cycles 2 - 3	1, 8, 15, 22	48 mg
Every two weeks	Cycles 4 - 9	1, 15	48 mg
Every four weeks	Cycles 10 +	1	48 mg
[a]0.16 mg is a priming dose, 0.8 mg is an intermediate dose and 48 mg is a full dose.			

Tepkinly should be administered until disease progression or unacceptable toxicity.

Details on recommended pre-medication for cytokine release syndrome (CRS) are shown in Table 2.

Table 2 Epcoritamab pre-medication

Cycle	Patient requiring pre-medication	Pre-medication	Administration
Cycle 1	All patients	Prednisolone (100 mg oral or intravenous) or dexamethasone (15 mg oral or intravenous) or equivalent	• 30-120 minutes prior to each weekly administration of epcoritamab • And for three consecutive days following each weekly administration of epcoritamab in Cycle 1
		• Diphenhydramine (50 mg oral or intravenous) or equivalent • Paracetamol (650 to 1 000 mg oral)	• 30-120 minutes prior to each weekly administration of epcoritamab
Cycle 2 and beyond	Patients who experienced Grade 2 or 3[a] CRS with previous dose	Prednisolone (100 mg oral or intravenous) or dexamethasone (15 mg oral or intravenous) or equivalent	• 30-120 minutes prior to next administration of epcoritamab after a grade 2 or 3[a] CRS event • And for three consecutive days following the next administration of epcoritamab until epcoritamab is given without subsequent CRS of Grade 2 or higher
[a]Patients will be permanently discontinued from epcoritamab after a Grade 4 CRS event.			

Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) and herpes virus infections is strongly recommended especially during concurrent use of steroids.

Tepkinly should be administered to adequately hydrated patients. Patients at an increased risk for clinical tumour lysis syndrome (CTLS) are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent.

Patients should be monitored for signs and symptoms of CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS) following epcoritamab administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS and/or ICANS. Patients should be counselled on the signs and symptoms associated with CRS and ICANS and on seeking immediate medical attention should signs or symptoms occur at any time (see section 4.4).

Dose modifications and management of adverse reactions

Cytokine release syndrome (CRS)
Patients treated with epcoritamab may develop CRS.
Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 3. Patients who experience CRS should be monitored more frequently during next scheduled epcoritamab administration.

Table 3 CRS grading and management guidance

Grade[a]	**Recommended therapy**	**Epcoritamab dose modification**
Grade 1 • Fever (temperature ≥ 38 °C)	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[b] may be initiated In cases of advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics • Anti-cytokine therapy, tocilizumab[d], should be considered For CRS with concurrent ICANS refer to **Table 4**	Hold epcoritamab until resolution of CRS event
Grade 2 • Fever (temperature ≥ 38 °C) and • Hypotension not requiring vasopressors and/or • Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[b] should be considered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 4**	Hold epcoritamab until resolution of CRS event

Grade[a]	Recommended therapy	Epcoritamab dose modification
Grade 3 • Fever (temperature ≥ 38 °C) and • Hypotension requiring a vasopressor with or without vasopressin and/or • Hypoxia requiring high-flow oxygen[f] by nasal cannula, facemask, non-rebreather mask, or venturi mask	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[c] should be administered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 4**	Hold epcoritamab until resolution of CRS event In the event of Grade 3 CRS lasting longer than 72 hours, epcoritamab should be discontinued If more than 2 separate events of Grade 3 CRS, even if each event resolved to Grade 2 within 72 hours, epcoritamab should be discontinued
Grade 4 • Fever (temperature ≥ 38 °C) and • Hypotension requiring ≥ 2 vasopressors (excluding vasopressin) and/or • Hypoxia requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[c] should be administered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 4**	Permanently discontinue epcoritamab

[a]CRS graded according to ASTCT consensus criteria
[b]Dexamethasone should be administered at 10-20 mg per day (or equivalent)
[c]Dexamethasone should be administered at 10-20 mg intravenously every 6 hours
[d]Tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period
[e]Low-flow oxygen is defined as oxygen delivered at < 6 L/minute
[f]High-flow oxygen is defined as oxygen delivered at ≥ 6 L/minute
[g]Riegler L et al. (2019)

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients should be monitored for signs and symptoms of ICANS. Other causes of neurologic symptoms should be ruled out. If ICANS is suspected, manage according to the recommendations in Table 4.

Table 4 ICANS grading and management guidance

Grade[a]	**Recommended therapy**	**Epcoritamab dose modification**
Grade 1[b] ICE score[c] 7-9[b] or, depressed level of consciousness[b]: awakens spontaneously	Treatment with dexamethasone[d] Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event
Grade 2[b] ICE score[c] 3-6 or, depressed level of consciousness[b]: awakens to voice	Treatment with dexamethasone[f] Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS*:* • Anti-cytokine therapy not recommended For ICANS with concurrent CRS*:* • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event
Grade 3[b] ICE score[c] 0-2 or, depressed level of consciousness[b]: awakens only to tactile stimulus, or seizures[b], either: • any clinical seizure, focal or generalised that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local	Treatment with dexamethasone[g] • If no response, initiate methylprednisolone 1 000 mg/day Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS*:* • Anti-cytokine therapy not recommended For ICANS with concurrent CRS*:* • Treatment with dexamethasone o If no response, initiate methylprednisolone 1 000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Permanently discontinue epcoritamab

Grade[a]	Recommended therapy	Epcoritamab dose modification
oedema[b] on neuroimaging[c]		
Grade 4[b] ICE score[c, b] 0 or, depressed level of consciousness[b] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[b], either: • life-threatening prolonged seizure (> 5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[b]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure / cerebral oedema[b], with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilloedema, or • cushing's triad	Treatment with dexamethasone[g] • If no response, initiate methylprednisolone 1 000 mg/day Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone o If no response, initiate methylprednisolone 1 000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Permanently discontinue epcoritamab

[a]ICANS graded according to ASTCT ICANS Consensus Grading
[b]ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral oedema) not attributable to any other cause
[c]If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
[d]Dexamethasone should be administered at 10 mg intravenously every 12 hours
[e]Riegler L et al. (2019)
[f]Dexamethasone 10-20 mg intravenously every 12 hours
[g]Dexamethasone 10-20 mg intravenously every 6 hours

Table 5 Recommended dose modifications for other adverse reactions

Adverse Reaction[1]	**Severity**[1]	**Action**
Infections (see section 4.4)	Grades 1-4	• Withhold epcoritamab in patients with active infection, until the infection resolves • For Grade 4, consider permanent discontinuation of Tepkinly
Neutropenia or febrile neutropenia (see section 4.8)	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold epcoritamab until absolute neutrophil count is 0.5 x 10^9/L or higher
Thrombocytopenia (see section 4.8)	Platelet count less than 50 x 10^9/L	• Withhold epcoritamab until platelet count is 50 x 10^9/L or higher
Other adverse reactions (see section 4.8)	Grade 3 or higher	• Withhold epcoritamab until the toxicity resolves to Grade 1 or baseline
[1]Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.		

Missed or delayed dose
A re-priming Cycle (identical to Cycle 1 with standard CRS prophylaxis) is required:

- If there are more than 8 days between the priming dose (0.16 mg) and intermediate dose (0.8 mg), or
- If there are more than 14 days between the intermediate dose (0.8 mg) and first full dose (48 mg), or
- If there are more than 6 weeks between full doses (48 mg)

After the re-priming cycle, the patient should resume treatment with Day 1 of the next planned treatment cycle (subsequent to the cycle during which the dose was delayed).

Special populations

Renal impairment

Dose adjustments are not considered necessary in patients with mild to moderate renal impairment. Epcoritamab has not been studied in patients with severe renal impairment to end stage renal disease. No dose recommendations can be made for patients with severe renal impairment to end-stage renal disease (see section 5.2).

Hepatic impairment

Dose adjustments are not considered necessary in patients with mild hepatic impairment. Epcoritamab has not been studied in patients with severe hepatic impairment (defined as total bilirubin > 3 times ULN and any AST) and data are limited in patients with moderate hepatic impairment (defined as total bilirubin > 1.5 to 3 times ULN and any AST). No dose recommendations can be made for patients with moderate to severe hepatic impairment (see section 5.2).

Elderly

No dose adjustment is necessary in patients ≥ 65 years of age (see sections 5.1 and 5.2).

Paediatric population

The safety and efficacy of Tepkinly in children aged less than 18 years of age have not yet been established. No data are available.

Method of administration

Tepkinly is for subcutaneous use. It should be administered by subcutaneous injection only, preferably in the lower part of the abdomen or the thigh. Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

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)

CRS, which may be life-threatening or fatal, occurred in patients receiving epcoritamab. The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS in more than two patients include chills, tachycardia, headache and dyspnoea.

Most CRS events occurred in Cycle 1 and were associated with the first full dose of epcoritamab. Administer prophylactic corticosteroids to mitigate the risk of CRS (see section 4.2).

Patients should be monitored for signs and symptoms of CRS following epcoritamab administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS. At the first signs or symptoms of CRS, treatment should be instituted of supportive care with tocilizumab and/or corticosteroids as appropriate (see section 4.2, Table 3). Patients should be counselled on the signs and symptoms associated with CRS and patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Management of CRS may require either temporary delay or discontinuation of epcoritamab based on the severity of CRS (see section 4.2).

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS, including a fatal event, have occurred in patients receiving epcoritamab. ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

The majority of cases of ICANS occurred within Cycle 1 of epcoritamab treatment, however some occurred with delayed onset.

Patients should be monitored for signs and symptoms of ICANS following epcoritamab administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of ICANS. At the first signs or symptoms of ICANS, treatment with corticosteroids and non-sedating-anti-seizure medicinal products should be instituted as appropriate (see section 4.2). Patients should be counselled on the signs and symptoms of ICANS and that the onset of events may be delayed. Patients should be instructed to contact their healthcare professional and seek

immediate medical attention should signs or symptoms occur at any time. Epcoritamab should be delayed or discontinued as recommended (see section 4.2).

Serious infections

Treatment with epcoritamab may lead to an increased risk of infections. Serious or fatal infections were observed in patients treated with epcoritamab in clinical studies (see section 4.8).

Administration of epcoritamab should be avoided in patients with clinically significant active systemic infections.
As appropriate, prophylactic antimicrobials should be administered prior to and during treatment with epcoritamab (see section 4.2). Patients should be monitored for signs and symptoms of infection, before and after epcoritamab administration, and treated appropriately. In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids and other supportive care, according to local guidelines.

Tumour lysis syndrome (TLS)

TLS has been reported in patients receiving epcoritamab (see section 4.8). Patients at an increased risk for TLS are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

Tumour flare

Tumour flare has been reported in patients treated with epcoritamab (see section 4.8). Manifestations could include localised pain and swelling. Consistent with the mechanism of action of epcoritamab, tumour flare is likely due to the influx of T-cells into tumour sites following epcoritamab administration.

There are no specific risk factors for tumour flare that have 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. Patients treated with epcoritamab should be monitored and evaluated for tumour flare at critical anatomical sites.

CD20-negative disease

There are limited data available on patients with CD20-negative DLBCL treated with Tepkinly, 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 Tepkinly should be considered.

Patient card

The doctor must inform the patient of the risk of CRS and ICANS and any signs and symptoms of CRS and ICANS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS and/or ICANS. Patients should be provided with a patient card and instructed to carry the card at all times. This card describes symptoms of CRS and ICANS which, if experienced, should prompt the patient to seek immediate medical attention.

Immunisation

Live and/or live-attenuated vaccines should not be given during epcoritamab therapy. Studies have not been conducted in patients who received live vaccines.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicinal product contains 21.9 mg of sorbitol per vial, which is equivalent to 27.33 mg/ml.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Transient elevation of certain proinflammatory cytokines by epcoritamab may suppress CYP450 enzyme activities. On initiation of epcoritamab therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should be advised to use effective contraception during treatment with epcoritamab and for at least 4 months after the last dose. Verify pregnancy status in females of reproductive potential prior to initiating epcoritamab treatment.

Pregnancy

Based on its mechanism of action, epcoritamab may cause foetal harm, including B-cell lymphocytopenia and alterations in normal immune responses, when administered to pregnant women. There are no data on the use of epcoritamab in pregnant women. Animal reproduction studies have not been conducted with epcoritamab. IgG1 antibodies, such as epcoritamab, can cross the placenta resulting in foetal exposure. Advise pregnant women of the potential risk to a foetus. Epcoritamab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether epcoritamab is excreted in human milk or its effect on milk production. Since IgGs are known to be present in milk, neonatal exposure to epcoritamab may occur via lactational transfer. Breast-feeding should be discontinued during treatment with epcoritamab and for at least4 months after the last dose.

Fertility

No fertility studies have been conducted with epcoritamab (see section 5.3). The effect of epcoritamab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Epcoritamab has minor influence on the ability to drive and use machines. Due to the potential for ICANS, patients should be advised to exercise caution while (or avoid if symptomatic) driving, cycling or using heavy or potentially dangerous machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of epcoritamab was evaluated in a non-randomised, single-arm study in 167 patients with relapsed or refractory LBCL after two or more lines of systemic therapy and included all the patients who enrolled to the 48 mg dose and received at least one dose of epcoritamab.

The median duration of exposure to epcoritamab was 3.7 months (range: 0 to 25 months).

The most common adverse reactions (≥ 20%) were CRS, fatigue, neutropenia, injection site reactions, musculoskeletal pain, abdominal pain, pyrexia, nausea and diarrhoea.

Serious adverse reactions occurred in 52% of patients. The most frequent serious adverse reaction (≥ 10%) was cytokine release syndrome (31%). Seven patients (4.2%) experienced a fatal adverse reaction (pneumonia in 3 (1.8%) patients, viral infection in 3 (1.8%) patients, and ICANS in 1 (0.6%) patient).

Adverse reactions that led to discontinuation occurred in 6.6% of patients. Discontinuation of epcoritamab due to pneumonia occurred in 6 (3.6%) patients, viral infection in 3 (1.8%) patients, and CRS, ICANS, or fatigue in 1 (0.6%) patient each.

Dose delays due to adverse reactions occurred in 32% of patients. Adverse reactions leading to dose delays (≥ 3%) were viral infections (9.6%), CRS (7.2%), neutropenia (4.8%), pyrexia (3.0%), and thrombocytopenia (3.0%).

Tabulated list of adverse reactions

Adverse reactions for epcoritamab from clinical studies (Table 6) are listed by MedDRA system organ class and are based on the following convention: 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); and very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6 Adverse reactions reported in patients with relapsed or refractory LBCL treated with epcoritamab in GCT3013-01 study

System organ class / preferred term or adverse reaction	All grades	Grade 3-4
Infections and infestations		
Viral infection[a]	Very common	Common
Pneumonia[b]	Very common	Common
Upper respiratory tract infection[c]	Common	Common
Fungal infections[d]	Common	
Sepsis[e]	Common	Common
Cellulitis	Common	Common
Neoplasm benign, malignant and unspecified (including cysts and polyps)		
Tumour flare	Common	
Blood and lymphatic system disorders		
Neutropenia[f]	Very common	Very common
Anaemia[g]	Very common	Very common
Thrombocytopenia[h]	Very common	Common
Lymphopenia[i]	Common	Common
Febrile neutropenia	Common	Common
Immune system disorders		
Cytokine release syndrome[j]	Very common	Common
Metabolism and nutrition disorders		
Decreased appetite	Very common	Uncommon
Hypophosphatemia	Common	Common
Hypokalemia	Common	Uncommon
Hypomagnesemia	Common	
Tumour lysis syndrome[k]	Common	Common
Nervous system disorders		
Headache	Very common	Uncommon
Immune effector cell-associated neurotoxicity syndrome[j]	Common	
Cardiac disorders		
Cardiac arrhythmias[l]	Very common	Common
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	Common	Common
Gastrointestinal disorders		
Abdominal pain[m]	Very common	Common
Nausea	Very common	Common
Diarrhoea	Very common	
Vomiting	Very common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[n]	Common	
Pruritus	Common	
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[o]	Very common	Common
General disorders and administration site conditions		
Fatigue[p]	Very common	Common
Injection site reactions[q]	Very common	
Pyrexia[r]	Very common	Uncommon
Oedema[s]	Very common	Common
Investigations		
Alanine aminotransferase increased	Common	Uncommon
Aspartate aminotransferase increased	Common	Common
Blood creatinine increased	Common	

Blood sodium decreased[t]	Common	Uncommon
Alkaline phosphatase increased	Common	

Adverse reactions were graded using NCI CTCAE version 5.0
[a]Viral infection includes asymptomatic COVID-19, COVID-19, cytomegalovirus infection, cytomegalovirus infection reactivation, gastroenteritis viral, herpes simplex, herpes zoster, and oral herpes
[b]Pneumonia includes COVID-19 pneumonia and pneumonia
[c]Upper respiratory tract infection includes laryngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, rhinovirus infection, and upper respiratory tract infection
[d]Fungal infection includes candida infection, oesophageal candidiasis, and oral candidiasis
[e]Sepsis includes bacteraemia, sepsis, and septic shock
[f]Neutropenia includes neutropenia and neutrophil count decreased
[g]Anaemia includes anaemia and serum ferritin decreased
[h]Thrombocytopenia includes platelet count decreased and thrombocytopenia
[i]Lymphopenia includes lymphocyte count decreased and lymphopenia
[j]CRS and ICANS adverse reactions were graded based on American Society for Transplantation and Cellular Therapy (ASTCT) criteria
[k]Tumour Lysis Syndrome was graded based on Cairo-Bishop
[l]Cardiac arrhythmias include bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia
[m]Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness
[n]Rash includes rash, rash erythematous, rash maculo-papular, and rash pustular
[o]Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, and spinal pain
[p]Fatigue includes asthenia, fatigue, and lethargy
[q]Injection site reactions include injection site bruising, injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, and injection site urticaria.
[r]Pyrexia includes body temperature increased and pyrexia
[s]Oedema includes face oedema, generalised oedema, oedema, oedema peripheral, and peripheral swelling
[t]Blood sodium decreased includes blood sodium decreased and hyponatraemia

Description of selected adverse reactions

Cytokine release syndrome

CRS of any grade occurred in 51% (85/167) of patients treated with epcoritamab. The incidence of Grade 1 was 31%, Grade 2 was 17%, and Grade 3 occurred in 3.0% of patients. Recurrent CRS occurred in 17% of patients. CRS of any grade occurred in 6.6% of patients after the priming dose (Cycle 1 Day 1); 13% after the intermediate dose (Cycle 1, Day 8); 44% after the first full dose (Cycle 1, Day 15), 4.6% after the second full dose (Cycle 1 Day 22) and 2.8% after the third full dose (Cycle 2 Day 1) or beyond. The median time to onset of CRS from the most recent administered epcoritamab dose was 2 days (range: 1 to 11 days). The median time to onset after the first full dose was 20.2 hours (range: 0.2 to 7 days). CRS resolved in 100% of patients, and the median duration of CRS events was 2 days (range 0.1 to 27 days).

Of the 85 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia 99%, hypotension 31% and hypoxia 19%. Other signs and symptoms of CRS in greater than two patients included chills (11%), tachycardia (including sinus tachycardia (9%)), dyspnoea (3.5%), and headache (3.5%). Transient elevated liver enzymes (ALT or AST > 3xULN) were concurrent with CRS in 2.4% of patients with CRS. See section 4.2 and 4.4 for monitoring and management guidance.

Immune effector cell-associated neurotoxicity syndrome

ICANS occurred in 6.0% of patients treated with epcoritamab; 4.2% experienced Grade 1 and 1.2% experienced Grade 2. One patient (0.6%) experienced an ICANS event of Grade 5 (fatal). The median time to first ICANS onset from the start of epcoritamab treatment (Cycle 1 Day 1) was 16.5 days (range: 8 to 141 days). ICANS resolved in 90% (9/10) of patients with supportive care. The median time to resolution of ICANS was 5 days (range: 1 to 9 days). In the 10 patients with ICANS, the onset of ICANS was prior to CRS in 20% of patients, concurrent with CRS in 40%, following onset of CRS in 10%, and in the absence of CRS in 30%.

Serious infections

Serious infections of any grade occurred in 25% of patients treated with epcoritamab. The most frequent serious infections included COVID-19 (6.6%), COVID-19 pneumonia (4.2%), pneumonia (3.6%), sepsis (2.4%), upper respiratory tract infection (1.8%), bacteraemia (1.2%), and septic shock (1.2%). The median time to onset of first serious infection from the start of epcoritamab treatment (Cycle 1 Day 1) was 56 days (range: 4 to 631 days), with median duration of 15 days (range: 4 to 125 days). Grade 5 events of infections occurred in 7 (4.2%) patients.

Neutropenia
Neutropenia of any grade occurred in 31% of patients, including 23% Grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased event was 65 days (range: 1 to 750 days), with median duration of 15 days (range: 2 to 155 days). Of the 51 patients who had neutropenia/neutrophil count decreased events, 51% received G-CSF to treat the events.

Tumour lysis syndrome
TLS occurred in 1.8% of patients. There was one patient who experienced onset on Day 14 with resolution on Day 17. Two additional patients experienced onset on Day 8 and Day 33 and both events were ongoing at the time of death; the deaths were due to disease progression.

Tumour flare
Tumour flare occurred in 3.0% of patients, all of which were grade 2. The median time to onset was 17 days (range 9 to 34 days), and median duration was 15.5 days (range 1 to 50 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

In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: not yet assigned

Mechanism of action

Epcoritamab is a humanised IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells.

Epcoritamab Fc region is silenced to prevent target-independent immune effector mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).

Pharmacodynamic effects

Epcoritamab induced rapid and sustained depletion of circulating B-cells (defined as CD19 B-cell counts < 10 cell/µl in the subjects who have detectable B cells at treatment initiation). There were 21% subjects (n=33) who had detectable circulating B-cells at treatment initiation. Transient reduction in circulating T cells was observed immediately after each dose in Cycle 1 and followed by T cell expansion in subsequent cycles.

Following subcutaneous administration of epcoritamab, transient and modest elevations of circulating levels of selected cytokines (IFN-γ, TNFα, IL-6, IL-2, and IL-10) occurred mostly after the first full dose (48 mg), with peak levels between 1 to 4 days post dose. Cytokine levels returned to baseline prior to the next full dose, however elevations of cytokines could also be observed after Cycle 1.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. The incidence of treatment-emergent ADAs at the approved 48 mg dosing regimen in the target DLBCL population was 2.9% (2.9% positive, 2.9% indeterminate and 94.3% negative, N=140 evaluable patients) and 2.6% (2.6% positive, 2.6% indeterminate and 94.9% negative, N= 39 evaluable patients), in studies GCT3013-01 and GCT3013-04, respectively. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited. Neutralising antibodies were not evaluated.

Clinical efficacy and safety

Study GCT3013-01 was an open-label, multi-cohort, multicentre, single-arm study that evaluated epcoritamab as monotherapy in patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL). The study includes a dose escalation part and an expansion part. The expansion part of the study included an aggressive non-Hodgkin lymphoma (aNHL) cohort, an indolent NHL (iNHL) cohort and a mantle-cell lymphoma (MCL) cohort. The pivotal aNHL cohort consisted of patients with LBCL (N=157), including patients with DLBCL (N=139, 12 patients of which had MYC, BCL2, and/or BCL6 rearrangements i.e., DH/TH), with high-grade B-cell lymphoma (HGBCL) (N=9), with follicular lymphoma grade 3B (FL) (N=5) and patients with primary mediastinal B-cell lymphoma (PMBCL) (N=4). In the DLBCL cohort, 29% (40/139) of patients had transformed DLBCL arising from indolent lymphoma. Patients included in the study were required to have documented CD20+ mature B-cell neoplasm according to WHO classification 2016 or WHO classification 2008 based on representative pathology report, failed prior autologous hematopoietic stem cell transplantation (HSCT) or were ineligible for autologous HSCT, patients who had lymphocyte counts < 5×10^9/L, and patients with at least 1 prior anti-CD20 monoclonal antibody-containing therapy.
The study excluded patients with central nervous system (CNS) involvement of lymphoma, prior treatment with allogeneic HSCT or solid organ transplant, chronic ongoing infectious diseases, any patients with known impaired T-cell immunity, a creatinine clearance of less than 45 ml/min, alanine aminotransferase > 3 times the upper limit of normal, cardiac ejection fraction less than 45%, and known clinically significant cardiovascular disease. Efficacy was evaluated in 139 patients with DLBCL who had received at least one dose of epcoritamab SC in cycles of 4 weeks, i.e., 28 days. Epcoritamab monotherapy was administered as follows:

- Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22
- Cycles 2-3: epcoritamab 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: epcoritamab 48 mg on Days 1 and 15
- Cycles 10 and beyond: epcoritamab 48 mg on Day 1

Patients continued to receive epcoritamab until disease progression or unacceptable toxicity.

The demographics and baseline characteristics are shown in Table 7.

Table 7 Demographics and baseline characteristics of patients with DLBCL in GCT3013-01 study

Characteristics	**(N=139)**
Age	
Median, years (min, max)	66 (22, 83)
< 65 years, n (%)	66 (47)
65 to < 75 years, n (%)	44 (32)
≥ 75 years, n (%)	29 (21)
Males, n (%)	85 (61)
Race, n (%)	
White	84 (60)
Asian	27 (19)
Other	5 (4)
Not Reported	23 (17)
ECOG performance status; n (%)	
0	67 (48)
1	67 (48)
2	5 (4)
Disease stage[c] at initial diagnosis, n (%)	
III	16 (12)
IV	86 (62)
Number of prior lines of anti-lymphoma therapy	
Median (min, max)	3 (2, 11)
2, n (%)	41 (30)
3, n (%)	47 (34)
≥ 4, n (%)	51 (37)
DLBCL Disease history; n (%)	
De Novo DLBCL	97 (70)
DLBCL transformed from indolent lymphoma	40 (29)
FISH Analysis Per Central lab[d], N=88	
Double-hit/Triple-hit lymphoma, n (%)	12 (14)
Prior autologous HSCT	26 (19)
Prior therapy; n (%)	
Prior CAR-T	53 (38)
Primary refractory disease[a]	82 (59)
Refractory to ≥ 2 consecutive lines of prior anti-lymphoma therapy[b]	104 (75)
Refractory to the last line of systemic antineoplastic therapy[b]	114 (82)
Refractory to prior anti-CD20 therapy	117 (84)
Refractory to CAR-T	39 (28)

[a]A patient is considered to be primary refractory if the patient is refractory to frontline anti-lymphoma therapy.
[b]A patient is considered to be refractory if the patient either experiences disease progression during therapy or disease progression within < 6 months after therapy completion. A patient is considered relapsed if the patient had recurred disease ≥ 6 months after therapy completion.
[c]Per Ann Arbor Staging.
[d]Post hoc central lab FISH analysis was performed on available diagnostic

baseline tumour tissue sections from 88 DLBCL patients.

The primary efficacy endpoint was overall response rate (ORR) determined by Lugano criteria (2014) as assessed by Independent Review Committee (IRC). The median follow-up time was 10.7 months (range: 0.3 to 17.9 months). The median duration of exposure was 4.1 months (range: 0 to 18 months).

Table 8 Efficacy results in study GCT3013-01 in patients with DLBCL[a]

Endpoint **IRC assessment**	**Epcoritamab** **(N=139)**
ORR[b], n (%)	86 (62)
(95% CI)	(53.3, 70)
CR[b], n (%)	54 (39)
(95% CI)	(30.7, 47.5)
PR, n (%)	32 (23)
(95% CI)	(16.3, 30.9)
DOR[b]	
Median (95% CI), months	15.5 (9.7, NR)
DOCR[b]	
Median (95% CI), months	NR (12.0, NR)
TTR, median (range), months	1.4 (1, 8.4)
CI = confidence interval; CR = complete response; DOR = duration of response; DOCR = duration of complete response; IRC = independent review committee; ORR = overall response rate; PR = partial response; TTR = time to response [a]Determined by Lugano criteria (2014) as assessed by independent review committee (IRC) [b]Included patients with initial PD by Lugano or IR by LYRIC who later obtained PR/CR.	

The median time to CR was 2.6 months (range: 1.2 to 10.2 months).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with epcoritamab in one or more subsets of the paediatric population in the treatment of mature B-cell malignancies, as per paediatric investigation plan (PIP) decision, for the granted indication (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

The population pharmacokinetics following subcutaneous administration of epcoritamab was described by a two-compartment model with first order subcutaneous absorption and target-mediated drug elimination. The moderate to high pharmacokinetic variability for epcoritamab was observed and characterised by inter-individual variability (IIV) ranging from 25.7% to 137.5% coefficient of variation (CV) for epcoritamab PK parameters.

Based on individually estimated exposures using population pharmacokinetic modelling, following the recommended SC dose of epcoritamab 48 mg, the geometric mean (% CV) C_{max} of epcoritamab is

10.8 mcg/ml (41.7%) and AUC0-7d is 68.9 day*mcg/ml (45.1%) at the end of the weekly dosing schedule. The C_{trough} at Week 12 is 8.4 (53.3%) mcg/ml.

The geometric mean (% CV) C_{max} of epcoritamab is 7.52 mcg/ml (41.1%) and AUC0-14d is 82.6 day*mcg/ml (49.3%) at the end of q2w schedule. The C_{trough} for q2W schedule is 4.1 (73.9%) mcg/ml.

The geometric mean (% CV) C_{max} of epcoritamab is 4.76 mcg/ml (51.6%) and AUC0-28d is 74.3 day*mcg/ml (69.5%) at steady state during the q4w schedule. The C_{trough} for q4W schedule is 1.2 (130%) mcg/ml.

Absorption

The peak concentrations occurred around 3-4 days (T_{max}) in patients with LBCL receiving the 48 mg full dose.

Distribution

The geometric mean (% CV) central volume of distribution is 8.27 l (27.5%) and apparent steady-state volume of distribution is 25.6 l (81.8%) based on population PK modelling.

Biotransformation

The metabolic pathway of epcoritamab has not been directly studied. Like other protein therapeutics, epcoritamab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

Epcoritamab is expected to undergo saturable target mediated clearance. The geometric mean (% CV) clearance (l/day) is 0.441 (27.8%). The half-life of epcoritamab is concentration dependent. The population PK model-derived geometric mean half-life of full dose epcoritamab (48 mg) ranged from 22 to 25 days based on frequency of dosing.

Special populations

No clinically important effects on the pharmacokinetics of epcoritamab (Cycle 1 AUC within approximately 36%) were observed based on age (20 to 89 years), sex, or race/ethnicity (white, Asian, and other), mild to moderate renal impairment creatinine clearance (CLcr ≥ 30 ml/min to CLcr < 90 ml/min), and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST) after accounting for differences in bodyweight. No patients with severe to end-stage renal disease (CLcr < 30 ml/min) or severe hepatic impairment (total bilirubin > 3 times ULN and any AST) have been studied. There is very limited data in moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN and any AST, N=1). Therefore, the pharmacokinetics of epcoritamab is unknown in these populations.

Like other therapeutic proteins, body weight (39 to 144 kg) has a statistically significant effect on the pharmacokinetics of epcoritamab. Based on exposure-response analysis and clinical data, considering the exposures in patients at either low body weight (e.g., 46 kg) or high body weight (e.g., 105 kg) and across body weight categories (< 65 kg, 65-< 85, ≥ 85), the effect on exposures is not clinically relevant.

Paediatric population

The pharmacokinetics of epcoritamab in paediatric patients has not been established.

5.3 Preclinical safety data

Animal pharmacology and/or toxicology

No reproductive or developmental toxicity studies in animals have been conducted with epcoritamab. Effects generally consistent with the pharmacologic mechanism of action of epcoritamab were observed in cynomolgus monkeys. These findings included dose-related adverse clinical signs (including vomiting, decreased activity, and mortality at high doses) and cytokine release, reversible hematologic alterations, reversible B-cell depletion in peripheral blood, and reversible decreased lymphoid cellularity in secondary lymphoid tissues.

Mutagenicity

Mutagenicity studies have not been conducted with epcoritamab.

Carcinogenicity

Carcinogenicity studies have not been conducted with epcoritamab.

Impairment of fertility

Animal fertility studies have not been conducted with epcoritamab, however, epcoritamab did not cause toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses up to 1 mg/kg/week in intravenous general toxicity study of 5-week duration. The AUC exposures (time-averaged over 7 days) at the high dose in cynomolgus monkeys were similar to those in patients (AUC0-7d) receiving the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products and/or diluents except those listed in section 6.6.

6.3 Shelf life

Unopened vial

2 years.

Diluted epcoritamab
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C including up to 12 hours at room temperature (20-25 °C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions 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.

Minimise exposure to daylight. Allow epcoritamab solution to equilibrate to room temperature before administration. Discard unused epcoritamab solution beyond the allowable storage time.

6.4 Special precautions for storage

Store and transport refrigerated (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

Type I glass vial with a bromobutyl rubber stopper coated with fluoropolymer at the contact site and aluminium seal with a plastic light blue flip off cap, containing 4 mg per 0.8 ml concentrate for solution for injection.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Epcoritamab must be prepared and administered by a healthcare provider as a subcutaneous injection.
Each vial of epcoritamab is intended for single use only.

Each vial contains an overfill that allows withdrawal of the labelled amount.

The administration of epcoritamab takes place over the course of 28-day cycles, following the dosing schedule in section 4.2.

Epcoritamab should be inspected visually for particulate matter and discolouration prior to administration. The concentrate should be a colourless to slightly yellow solution. Do not use if the solution is discoloured, or cloudy, or if foreign particles are present.

Preparation of epcoritamab
Epcoritamab has to be prepared using aseptic technique. Filtration of the diluted solution is not required.

Preparation instructions for 0.16 mg and 0.8 mg doses of epcoritamab
0.16 mg priming dose preparation instructions – **2 dilutions required**
Use an appropriately sized, syringe, vial, and needle for each transfer step.

1) Prepare epcoritamab vial a) Retrieve one 4 mg/0.8 ml epcoritamab vial with the **light blue** cap from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour. c) Gently swirl the epcoritamab vial. **DO NOT** vortex or vigorously shake the vial.
2) Perform first dilution a) Label an appropriately sized empty vial as **"dilution A"**. b) Transfer **0.8 ml of epcoritamab** into the **dilution A** vial. c) Transfer **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** vial. The initial diluted solution contains 0.8 mg/ml of epcoritamab. d) Gently swirl the **dilution A** vial for 30 – 45 seconds.
3) Perform second dilution a) Label an appropriately sized empty vial as **"dilution B"**. b) Transfer **2 ml of solution** from the **dilution A** vial into the **dilution B** vial. The **dilution A** vial is no longer needed and should be discarded.

c) Transfer **8 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution B** vial to make a final concentration of 0.16 mg/ml. d) Gently swirl the **dilution B** vial for 30 – 45 seconds.
4) Withdraw dose Withdraw **1 ml of the diluted epcoritamab** from the **dilution B** vial into a syringe. The **dilution B** vial is no longer needed and should be discarded.
5) Label syringe Label the syringe with the product name, dose strength (0.16 mg), date and the time of day. For storage of the diluted epcoritamab, see section 6.3.
6) Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

<u>0.8 mg intermediate dose preparation instructions – **1 dilution required**</u>
Use an appropriately sized syringe, vial and needle for each transfer step.

1) Prepare epcoritamab vial a) Retrieve one 4 mg/0.8 ml epcoritamab vial with the **light blue** cap from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour. c) Gently swirl the epcoritamab vial. **DO NOT** vortex or vigorously shake the vial.
2) Perform dilution a) Label an appropriately sized empty vial as **"dilution A"**. b) Transfer **0.8 ml of epcoritamab** into the **dilution A** vial. c) Transfer **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** vial to make a final concentration of 0.8 mg/ml. d) Gently swirl the **dilution A** vial for 30 – 45 seconds.
3) Withdraw dose Withdraw **1 ml of the diluted epcoritamab** from the **dilution A** vial into a syringe. The **dilution A** vial is no longer needed and should be discarded.
4) Label syringe Label the syringe with the product name, dose strength (0.8 mg), date and the time of day. For storage of the diluted epcoritamab, see section 6.3.
5) Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/23/1759/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

▼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

Tepkinly 48 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.8 ml vial contains 48 mg of epcoritamab at a concentration of 60 mg/ml.

Each vial contains an overfill that allows withdrawal of the labelled amount.

Epcoritamab is a humanised immunoglobulin G1 (IgG1)-bispecific antibody against CD3 and CD20 antigens, produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipient with known effect
Each vial of Tepkinly contains 21.9 mg of sorbitol. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Colourless to slightly yellow solution, pH 5.5 and osmolality of approximately 211 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tepkinly 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

Tepkinly must only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapy. At least 1 dose of tocilizumab for use in the event of CRS should be available prior to epcoritamab administration for Cycle 1. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose should be available.

Posology

Recommended pre-medication and dose schedule

Tepkinly should be administered according to the following dosing schedule in 28-day cycles which is outlined in Table 1.

Table 1 Dosing schedule

Dosing schedule	Cycle of treatment	Days	Epcoritamab dose (mg)[a]
Weekly	Cycle 1	1	0.16 mg (Step-up dose 1)
		8	0.8 mg (Step-up dose 2)
		15	48 mg (First full dose)
		22	48 mg
Weekly	Cycles 2 - 3	1, 8, 15, 22	48 mg
Every two weeks	Cycles 4 - 9	1, 15	48 mg
Every four weeks	Cycles 10 +	1	48 mg
[a]0.16 mg is a priming dose, 0.8 mg is an intermediate dose and 48 mg is a full dose.			

Tepkinly should be administered until disease progression or unacceptable toxicity.

Details on recommended pre-medication for cytokine release syndrome (CRS) are shown in Table 2.

Table 2 Epcoritamab pre-medication

Cycle	Patient requiring pre-medication	Pre-medication	Administration
Cycle 1	All patients	Prednisolone (100 mg oral or intravenous) or dexamethasone (15 mg oral or intravenous) or equivalent	• 30-120 minutes prior to each weekly administration of epcoritamab • And for three consecutive days following each weekly administration of epcoritamab in Cycle 1
		• Diphenhydramine (50 mg oral or intravenous) or equivalent • Paracetamol (650 to 1 000 mg oral)	• 30-120 minutes prior to each weekly administration of epcoritamab
Cycle 2 and beyond	Patients who experienced Grade 2 or 3[a] CRS with previous dose	Prednisolone (100 mg oral or intravenous) or dexamethasone (15 mg oral or intravenous) or equivalent	• 30-120 minutes prior to next administration of epcoritamab after a grade 2 or 3[a] CRS event • And for three consecutive days following the next administration of epcoritamab until epcoritamab is given without subsequent CRS of Grade 2 or higher
[a]Patients will be permanently discontinued from epcoritamab after a Grade 4 CRS event.			

Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) and herpes virus infections is strongly recommended especially during concurrent use of steroids.

Tepkinly should be administered to adequately hydrated patients. Patients at an increased risk for clinical tumour lysis syndrome (CTLS) are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent.

Patients should be monitored for signs and symptoms of CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS) following epcoritamab administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS and/or ICANS. Patients should be counselled on the signs and symptoms associated with CRS and ICANS and on seeking immediate medical attention should signs or symptoms occur at any time (see section 4.4).

Dose modifications and management of adverse reactions

Cytokine release syndrome (CRS)
Patients treated with epcoritamab may develop CRS.
Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 3. Patients who experience CRS should be monitored more frequently during next scheduled epcoritamab administration.

Table 3 CRS grading and management guidance

Grade[a]	Recommended therapy	Epcoritamab dose modification
Grade 1 • Fever (temperature ≥ 38 °C)	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[b] may be initiated In cases of advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics • Anti-cytokine therapy, tocilizumab[d], should be considered For CRS with concurrent ICANS refer to **Table 4**	Hold epcoritamab until resolution of CRS event
Grade 2 • Fever (temperature ≥ 38 °C) and • Hypotension not requiring vasopressors and/or • Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[b] should be considered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone	Hold epcoritamab until resolution of CRS event

Grade[a]	Recommended therapy	Epcoritamab dose modification
	1 000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 4**	
Grade 3 • Fever (temperature ≥ 38 °C) and • Hypotension requiring a vasopressor with or without vasopressin and/or • Hypoxia requiring high-flow oxygen[f] by nasal cannula, facemask, non-rebreather mask, or venturi mask	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[c] should be administered Anti-cytokine therapy, tocilizumab[d], is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 4**	Hold epcoritamab until resolution of CRS event In the event of Grade 3 CRS lasting longer than 72 hours, epcoritamab should be discontinued If more than 2 separate events of Grade 3 CRS, even if each event resolved to Grade 2 within 72 hours, epcoritamab should be discontinued
Grade 4 • Fever (temperature ≥ 38 °C) and Hypotension requiring ≥ 2 vasopressors (excluding vasopressin) and/or • Hypoxia requiring positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	Provide supportive care such as antipyretics and intravenous hydration Dexamethasone[c] should be administered Anti-cytokine therapy, tocilizumab[d] is recommended If CRS is refractory to dexamethasone and tocilizumab: • Alternative immunosuppressants[g] and methylprednisolone 1 000 mg/day intravenously should be administered until clinical improvement For CRS with concurrent ICANS refer to **Table 4**	Permanently discontinue epcoritamab

Grade[a]	Recommended therapy	Epcoritamab dose modification
[a]CRS graded according to ASTCT consensus criteria [b]Dexamethasone should be administered at 10-20 mg per day (or equivalent) [c]Dexamethasone should be administered at 10-20 mg intravenously every 6 hours [d]Tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period [e]Low-flow oxygen is defined as oxygen delivered at < 6 L/minute [f]High-flow oxygen is defined as oxygen delivered at ≥ 6 L/minute [g]Riegler L et al. (2019)		

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients should be monitored for signs and symptoms of ICANS. Other causes of neurologic symptoms should be ruled out. If ICANS is suspected, manage according to the recommendations in Table 4.

Table 4 ICANS grading and management guidance

Grade[a]	Recommended therapy	Epcoritamab dose modification
Grade 1[b] ICE score[c] 7-9[b] or, depressed level of consciousness[b]: awakens spontaneously	Treatment with dexamethasone[d] Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event
Grade 2[b] ICE score[c] 3-6 or, depressed level of consciousness[b]: awakens to voice	Treatment with dexamethasone[f] Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS*:* • Anti-cytokine therapy not recommended For ICANS with concurrent CRS*:* • Treatment with dexamethasone[d] • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Hold epcoritamab until resolution of event
Grade 3[b] ICE score[c] 0-2 or, depressed level of consciousness[b]: awakens only to tactile stimulus, or seizures[b], either:	Treatment with dexamethasone[g]. • If no response, initiate methylprednisolone 1 000 mg/day Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS*:*	Permanently discontinue epcoritamab

Grade[a]	Recommended therapy	Epcoritamab dose modification
• any clinical seizure, focal or generalised that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema[b] on neuroimaging[c]	• Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone o If no response, initiate methylprednisolone 1 000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	
Grade 4[b] ICE score[c, b] 0 or, depressed level of consciousness[b] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[b], either: • life-threatening prolonged seizure (> 5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[b]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure / cerebral oedema[b], with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilloedema, or • cushing's triad	Treatment with dexamethasone[g] • If no response, initiate methylprednisolone 1 000 mg/day Consider non-sedating anti-seizure medicinal products (e.g., levetiracetam) until resolution of ICANS No concurrent CRS: • Anti-cytokine therapy not recommended For ICANS with concurrent CRS: • Treatment with dexamethasone o If no response, initiate methylprednisolone 1 000 mg/day • Choose immunosuppressant alternatives[e] to tocilizumab, if possible	Permanently discontinue epcoritamab
[a]ICANS graded according to ASTCT ICANS Consensus Grading		

Grade[a]	Recommended therapy	Epcoritamab dose modification
[b]ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizures, motor findings, raised ICP/cerebral oedema) not attributable to any other cause [c]If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points. [d]Dexamethasone should be administered at 10 mg intravenously every 12 hours [e]Riegler L et al. (2019) [f]Dexamethasone 10-20 mg intravenously every 12 hours [g]Dexamethasone 10-20 mg intravenously every 6 hours		

Table 5 Recommended dose modifications for other adverse reactions

Adverse Reaction[1]	Severity[1]	Action
Infections (see section 4.4)	Grades 1-4	• Withhold epcoritamab in patients with active infection, until the infection resolves • For Grade 4, consider permanent discontinuation of Tepkinly
Neutropenia or febrile neutropenia (see section 4.8)	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold epcoritamab until absolute neutrophil count is 0.5 x 10^9/L or higher
Thrombocytopenia (see section 4.8)	Platelet count less than 50 x 10^9/L	• Withhold epcoritamab until platelet count is 50 x 10^9/L or higher
Other adverse reactions (see section 4.8)	Grade 3 or higher	• Withhold epcoritamab until the toxicity resolves to Grade 1 or baseline
[1]Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.		

Missed or delayed dose

A re-priming Cycle (identical to Cycle 1 with standard CRS prophylaxis) is required:

- If there are more than 8 days between the priming dose (0.16 mg) and intermediate dose (0.8 mg), or
- If there are more than 14 days between the intermediate dose (0.8 mg) and first full dose (48 mg), or
- If there are more than 6 weeks between full doses (48 mg)

After the re-priming cycle, the patient should resume treatment with Day 1 of the next planned treatment cycle (subsequent to the cycle during which the dose was delayed).

Special populations

Renal impairment

Dose adjustments are not considered necessary in patients with mild to moderate renal impairment. Epcoritamab has not been studied in patients with severe renal impairment to end stage renal disease. No dose recommendations can be made for patients with severe renal impairment to end-stage renal disease (see section 5.2).

Hepatic impairment

Dose adjustments are not considered necessary in patients with mild hepatic impairment. Epcoritamab has not been studied in patients with severe hepatic impairment (defined as total bilirubin > 3 times ULN and any AST) and data are limited in patients with moderate hepatic impairment (defined as total bilirubin > 1.5 to 3 times ULN and any AST). No dose recommendations can be made for patients with moderate to severe hepatic impairment (see section 5.2).

Elderly

No dose adjustment is necessary in patients ≥ 65 years of age (see sections 5.1 and 5.2).

Paediatric population

The safety and efficacy of Tepkinly in children aged less than 18 years of age have not yet been established. No data are available.

Method of administration

Tepkinly is for subcutaneous use. It should be administered by subcutaneous injection only, preferably in the lower part of the abdomen or the thigh. Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

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)

CRS, which may be life-threatening or fatal, occurred in patients receiving epcoritamab. The most common signs and symptoms of CRS include pyrexia, hypotension and hypoxia. Other signs and symptoms of CRS in more than two patients include chills, tachycardia, headache and dyspnoea.

Most CRS events occurred in Cycle 1 and were associated with the first full dose of epcoritamab. Administer prophylactic corticosteroids to mitigate the risk of CRS (see section 4.2).

Patients should be monitored for signs and symptoms of CRS following epcoritamab administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of CRS. At the first signs or symptoms of CRS, treatment should be instituted of supportive care with tocilizumab and/or corticosteroids as appropriate (see section 4.2, Table 3). Patients should be counselled on the signs and symptoms associated with CRS and patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Management of CRS may require either temporary delay or discontinuation of epcoritamab based on the severity of CRS (see section 4.2).

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS, including a fatal event, have occurred in patients receiving epcoritamab. ICANS may manifest as aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

The majority of cases of ICANS occurred within Cycle 1 of epcoritamab treatment, however some occurred with delayed onset.

Patients should be monitored for signs and symptoms of ICANS following epcoritamab administration. Patients should be hospitalised for 24 hours after administration of the Cycle 1 Day 15 dose of 48 mg to monitor for signs and symptoms of ICANS. At the first signs or symptoms of ICANS, treatment with corticosteroids and non-sedating-anti-seizure medicinal products should be instituted as appropriate (see section 4.2). Patients should be counselled on the signs and symptoms of ICANS and that the onset of events may be delayed. Patients should be instructed to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Epcoritamab should be delayed or discontinued as recommended (see section 4.2).

Serious infections

Treatment with epcoritamab may lead to an increased risk of infections. Serious or fatal infections were observed in patients treated with epcoritamab in clinical studies (see section 4.8).

Administration of epcoritamab should be avoided in patients with clinically significant active systemic infections.
As appropriate, prophylactic antimicrobials should be administered prior to and during treatment with epcoritamab (see section 4.2). Patients should be monitored for signs and symptoms of infection, before and after epcoritamab administration, and treated appropriately. In the event of febrile neutropenia, patients should be evaluated for infection and managed with antibiotics, fluids and other supportive care, according to local guidelines.

Tumour lysis syndrome (TLS)

TLS has been reported in patients receiving epcoritamab (see section 4.8). Patients at an increased risk for TLS are recommended to receive hydration and prophylactic treatment with a uric acid lowering agent. Patients should be monitored for signs or symptoms of TLS, especially patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function. Patients should be monitored for blood chemistries and abnormalities should be managed promptly.

Tumour flare

Tumour flare has been reported in patients treated with epcoritamab (see section 4.8). Manifestations could include localised pain and swelling. Consistent with the mechanism of action of epcoritamab, tumour flare is likely due to the influx of T-cells into tumour sites following epcoritamab administration.

There are no specific risk factors for tumour flare that have 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. Patients treated with epcoritamab should be monitored and evaluated for tumour flare at critical anatomical sites.

CD20-negative disease

There are limited data available on patients with CD20-negative DLBCL treated with Tepkinly, 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 Tepkinly should be considered.

Patient card

The doctor must inform the patient of the risk of CRS and ICANS and any signs and symptoms of CRS and ICANS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS and/or ICANS. Patients should be provided with a patient card and instructed to carry the card at all times. This card describes symptoms of CRS and ICANS which, if experienced, should prompt the patient to seek immediate medical attention.

Immunisation

Live and/or live-attenuated vaccines should not be given during epcoritamab therapy. Studies have not been conducted in patients who received live vaccines.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicinal product contains 21.9 mg of sorbitol per vial, which is equivalent to 27.33 mg/ml.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Transient elevation of certain proinflammatory cytokines by epcoritamab may suppress CYP450 enzyme activities. On initiation of epcoritamab therapy in patients being treated with CYP450 substrates with a narrow therapeutic index, therapeutic monitoring should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should be advised to use effective contraception during treatment with epcoritamab and for at least 4 months after the last dose. Verify pregnancy status in females of reproductive potential prior to initiating epcoritamab treatment.

Pregnancy

Based on its mechanism of action, epcoritamab may cause foetal harm, including B-cell lymphocytopenia and alterations in normal immune responses, when administered to pregnant women. There are no data on the use of epcoritamab in pregnant women. Animal reproduction studies have not been conducted with epcoritamab. IgG1 antibodies, such as epcoritamab, can cross the placenta resulting in foetal exposure. Advise pregnant women of the potential risk to a foetus. Epcoritamab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether epcoritamab is excreted in human milk or its effect on milk production. Since IgGs are known to be present in milk, neonatal exposure to epcoritamab may occur via lactational transfer. Breast-feeding should be discontinued during treatment with epcoritamab and for at least4 months after the last dose.

Fertility

No fertility studies have been conducted with epcoritamab (see section 5.3). The effect of epcoritamab on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Epcoritamab has minor influence on the ability to drive and use machines. Due to the potential for ICANS, patients should be advised to exercise caution while (or avoid if symptomatic) driving, cycling or using heavy or potentially dangerous machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of epcoritamab was evaluated in a non-randomised, single-arm study in 167 patients with relapsed or refractory LBCL after two or more lines of systemic therapy and included all the patients who enrolled to the 48 mg dose and received at least one dose of epcoritamab.

The median duration of exposure to epcoritamab was 3.7 months (range: 0 to 25 months).

The most common adverse reactions (≥ 20%) were CRS, fatigue, neutropenia, injection site reactions, musculoskeletal pain, abdominal pain, pyrexia, nausea, and diarrhoea.

Serious adverse reactions occurred in 52% of patients. The most frequent serious adverse reaction (≥ 10%) was cytokine release syndrome (31%). Seven patients (4.2%) experienced a fatal adverse reaction (pneumonia in 3 (1.8%) patients, viral infection in 3 (1.8%) patients, and ICANS in 1 (0.6%) patient).

Adverse reactions that led to discontinuation occurred in 6.6% of patients. Discontinuation of epcoritamab due to pneumonia occurred in 6 (3.6%) patients, viral infection in 3 (1.8%) patients, and CRS, ICANS, or fatigue in 1 (0.6%) patient each.

Dose delays due to adverse reactions occurred in 32% of patients. Adverse reactions leading to dose delays (≥ 3%) were viral infections (9.6%), CRS (7.2%), neutropenia (4.8%), pyrexia (3.0%), and thrombocytopenia (3.0%).

Tabulated list of adverse reactions

Adverse reactions for epcoritamab from clinical studies (Table 6) are listed by MedDRA system organ class and are based on the following convention: 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); and very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6 Adverse reactions reported in patients with relapsed or refractory LBCL treated with epcoritamab in GCT3013-01 study

System organ class / preferred term or adverse reaction	All grades	Grade 3-4
Infections and infestations		
Viral infection[a]	Very common	Common
Pneumonia[b]	Very common	Common
Upper respiratory tract infection[c]	Common	Common
Fungal infections[d]	Common	
Sepsis[e]	Common	Common
Cellulitis	Common	Common
Neoplasm benign, malignant and unspecified (including cysts and polyps)		
Tumour flare	Common	
Blood and lymphatic system disorders		
Neutropenia[f]	Very common	Very common
Anaemia[g]	Very common	Very common
Thrombocytopenia[h]	Very common	Common
Lymphopenia[i]	Common	Common
Febrile neutropenia	Common	Common
Immune system disorders		
Cytokine release syndrome[j]	Very common	Common
Metabolism and nutrition disorders		
Decreased appetite	Very common	Uncommon
Hypophosphatemia	Common	Common
Hypokalemia	Common	Uncommon
Hypomagnesemia	Common	
Tumour lysis syndrome[k]	Common	Common
Nervous system disorders		
Headache	Very common	Uncommon
Immune effector cell-associated neurotoxicity syndrome[j]	Common	
Cardiac disorders		
Cardiac arrhythmias[l]	Very common	Common
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	Common	Common
Gastrointestinal disorders		
Abdominal pain[m]	Very common	Common
Nausea	Very common	Common
Diarrhoea	Very common	
Vomiting	Very common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[n]	Common	
Pruritus	Common	
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[o]	Very common	Common
General disorders and administration site conditions		
Fatigue[p]	Very common	Common
Injection site reactions[q]	Very common	
Pyrexia[r]	Very common	Uncommon
Oedema[s]	Very common	Common
Investigations		
Alanine aminotransferase increased	Common	Uncommon

Aspartate aminotransferase increased	Common	Common
Blood creatinine increased	Common	
Blood sodium decreased[t]	Common	Uncommon
Alkaline phosphatase increased	Common	

Adverse reactions were graded using NCI CTCAE version 5.0
[a]Viral infection includes asymptomatic COVID-19, COVID-19, cytomegalovirus infection, cytomegalovirus infection reactivation, gastroenteritis viral, herpes simplex, herpes zoster, and oral herpes
[b]Pneumonia includes COVID-19 pneumonia and pneumonia
[c]Upper respiratory tract infection includes laryngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, rhinovirus infection, and upper respiratory tract infection
[d]Fungal infection includes candida infection, oesophageal candidiasis, and oral candidiasis
[e]Sepsis includes bacteraemia, sepsis, and septic shock
[f]Neutropenia includes neutropenia and neutrophil count decreased
[g]Anaemia includes anaemia and serum ferritin decreased
[h]Thrombocytopenia includes platelet count decreased and thrombocytopenia
[i]Lymphopenia includes lymphocyte count decreased and lymphopenia
[j]CRS and ICANS adverse reactions were graded based on American Society for Transplantation and Cellular Therapy (ASTCT) criteria
[k]Tumour Lysis Syndrome was graded based on Cairo-Bishop
[l]Cardiac arrhythmias include bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia
[m]Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness
[n]Rash includes rash, rash erythematous, rash maculo-papular, and rash pustular
[o]Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, and spinal pain
[p]Fatigue includes asthenia, fatigue, and lethargy
[q]Injection site reactions include injection site bruising, injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, and injection site urticaria.
[r]Pyrexia includes body temperature increased and pyrexia
[s]Oedema includes face oedema, generalised oedema, oedema, oedema peripheral, and peripheral swelling
[t]Blood sodium decreased includes blood sodium decreased and hyponatraemia

Description of selected adverse reactions

Cytokine release syndrome

CRS of any grade occurred in 51% (85/167) of patients treated with epcoritamab. The incidence of Grade 1 was 31%, Grade 2 was 17%, and Grade 3 occurred in 3.0% of patients. Recurrent CRS occurred in 17% of patients. CRS of any grade occurred in 6.6% of patients after the priming dose (Cycle 1 Day 1); 13% after the intermediate dose (Cycle 1, Day 8); 44% after the first full dose (Cycle 1, Day 15), 4.6% after the second full dose (Cycle 1 Day 22) and 2.8% after the third full dose (Cycle 2 Day 1) or beyond. The median time to onset of CRS from the most recent administered epcoritamab dose was 2 days (range: 1 to 11 days). The median time to onset after the first full dose was 20.2 hours (range: 0.2 to 7 days). CRS resolved in 100% of patients, and the median duration of CRS events was 2 days (range 0.1 to 27 days).

Of the 85 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia 99%, hypotension 31% and hypoxia 19%. Other signs and symptoms of CRS in greater than two patients included chills (11%), tachycardia (including sinus tachycardia (9%)), dyspnoea (3.5%), and headache (3.5%). Transient elevated liver enzymes (ALT or AST > 3xULN) were concurrent with CRS in 2.4% of patients with CRS. See section 4.2 and 4.4 for monitoring and management guidance.

Immune effector cell-associated neurotoxicity syndrome

ICANS occurred in 6.0% of patients treated with epcoritamab; 4.2% experienced Grade 1 and 1.2% experienced Grade 2. One patient (0.6%) experienced an ICANS event of Grade 5 (fatal). The median time to first ICANS onset from the start of epcoritamab treatment (Cycle 1 Day 1) was 16.5 days (range: 8 to 141 days). ICANS resolved in 90% (9/10) of patients with supportive care. The median time to resolution of ICANS was 5 days (range: 1 to 9 days). In the 10 patients with ICANS, the onset of ICANS was prior to CRS in 20% of patients, concurrent with CRS in 40%, following onset of CRS in 10%, and in the absence of CRS in 30%.

Serious infections

Serious infections of any grade occurred in 25% of patients treated with epcoritamab. The most frequent serious infections included COVID-19 (6.6%), COVID-19 pneumonia (4.2%), pneumonia (3.6%), sepsis (2.4%), upper respiratory tract infection (1.8%), bacteraemia (1.2%), and septic shock (1.2%). The median time to onset of first serious infection from the start of epcoritamab treatment (Cycle 1 Day 1) was 56 days (range: 4 to 631 days), with median duration of 15 days (range: 4 to 125 days). Grade 5 events of infections occurred in 7 (4.2%) patients.

Neutropenia
Neutropenia of any grade occurred in 31% of patients, including 23% Grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased event was 65 days (range: 1 to 750 days), with median duration of 15 days (range: 2 to 155 days). Of the 51 patients who had neutropenia/neutrophil count decreased events, 51% received G-CSF to treat the events.

Tumour lysis syndrome
TLS occurred in 1.8% of patients. There was one patient who experienced onset on Day 14 with resolution on Day 17. Two additional patients experienced onset on Day 8 and Day 33 and both events were ongoing at the time of death; the deaths were due to disease progression.

Tumour flare
Tumour flare occurred in 3.0% of patients, all of which were grade 2. The median time to onset was 17 days (range 9 to 34 days), and median duration was 15.5 days (range 1 to 50 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

In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: not yet assigned

Mechanism of action

Epcoritamab is a humanised IgG1-bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. The activity of epcoritamab is dependent upon simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells by epcoritamab that induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells.

Epcoritamab Fc region is silenced to prevent target-independent immune effector mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).

Pharmacodynamic effects

Epcoritamab induced rapid and sustained depletion of circulating B-cells (defined as CD19 B-cell counts < 10 cell/µl in the subjects who have detectable B cells at treatment initiation). There were 21% subjects (n=33) who had detectable circulating B-cells at treatment initiation. Transient reduction in circulating T cells was observed immediately after each dose in Cycle 1 and followed by T cell expansion in subsequent cycles.

Following subcutaneous administration of epcoritamab, transient and modest elevations of circulating levels of selected cytokines (IFN-γ, TNFα, IL-6, IL-2, and IL-10) occurred mostly after the first full dose (48 mg), with peak levels between 1 to 4 days post dose. Cytokine levels returned to baseline prior to the next full dose, however elevations of cytokines could also be observed after Cycle 1.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. The incidence of treatment-emergent ADAs at the approved 48 mg dosing regimen in the target DLBCL population was 2.9% (2.9% positive, 2.9% indeterminate and 94.3% negative, N=140 evaluable patients) and 2.6% (2.6% positive, 2.6% indeterminate and 94.9% negative, N= 39 evaluable patients), in studies GCT3013-01 and GCT3013-04, respectively. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited. Neutralising antibodies were not evaluated.

Clinical efficacy and safety

Study GCT3013-01 was an open-label, multi-cohort, multicentre, single-arm study that evaluated epcoritamab as monotherapy in patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL). The study includes a dose escalation part and an expansion part. The expansion part of the study included an aggressive non-Hodgkin lymphoma (aNHL) cohort, an indolent NHL (iNHL) cohort and a mantle-cell lymphoma (MCL) cohort. The pivotal aNHL cohort consisted of patients with LBCL (N=157), including patients with DLBCL (N=139, 12 patients of which had MYC, BCL2, and/or BCL6 rearrangements i.e., DH/TH), with high-grade B-cell lymphoma (HGBCL) (N=9), with follicular lymphoma grade 3B (FL) (N=5) and patients with primary mediastinal B-cell lymphoma (PMBCL) (N=4). In the DLBCL cohort, 29% (40/139) of patients had transformed DLBCL arising from indolent lymphoma. Patients included in the study were required to have documented CD20+ mature B-cell neoplasm according to WHO classification 2016 or WHO classification 2008 based on representative pathology report, failed prior autologous hematopoietic stem cell transplantation (HSCT) or were ineligible for autologous HSCT, patients who had lymphocyte counts < 5×10^9/L, and patients with at least 1 prior anti-CD20 monoclonal antibody-containing therapy.
The study excluded patients with central nervous system (CNS) involvement of lymphoma, prior treatment with allogeneic HSCT or solid organ transplant, chronic ongoing infectious diseases, any patients with known impaired T-cell immunity, a creatinine clearance of less than 45 ml/min, alanine aminotransferase > 3 times the upper limit of normal, cardiac ejection fraction less than 45%, and known clinically significant cardiovascular disease. Efficacy was evaluated in 139 patients with DLBCL who had received at least one dose of epcoritamab SC in cycles of 4 weeks, i.e., 28 days. Epcoritamab monotherapy was administered as follows:

- Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and Day 22
- Cycles 2-3: epcoritamab 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: epcoritamab 48 mg on Days 1 and 15
- Cycles 10 and beyond: epcoritamab 48 mg on Day 1

Patients continued to receive epcoritamab until disease progression or unacceptable toxicity.

The demographics and baseline characteristics are shown in Table 7.

Table 7 Demographics and baseline characteristics of patients with DLBCL in GCT3013-01 study

Characteristics	**(N=139)**
Age	
Median, years (min, max)	66 (22, 83)
< 65 years, n (%)	66 (47)
65 to < 75 years, n (%)	44 (32)
≥ 75 years, n (%)	29 (21)
Males, n (%)	85 (61)
Race, n (%)	
White	84 (60)
Asian	27 (19)
Other	5 (4)
Not Reported	23 (17)
ECOG performance status; n (%)	
0	67 (48)
1	67 (48)
2	5 (4)
Disease stage[c] at initial diagnosis, n (%)	
III	16 (12)
IV	86 (62)
Number of prior lines of anti-lymphoma therapy	
Median (min, max)	3 (2, 11)
2, n (%)	41 (30)
3, n (%)	47 (34)
≥ 4, n (%)	51 (37)
DLBCL Disease history; n (%)	
De Novo DLBCL	97 (70)
DLBCL transformed from indolent lymphoma	40 (29)
FISH Analysis Per Central lab[d], N=88	
Double-hit/Triple-hit lymphoma, n (%)	12 (14)
Prior autologous HSCT	26 (19)
Prior therapy; n (%)	
Prior CAR-T	53 (38)
Primary refractory disease[a]	82 (59)
Refractory to ≥ 2 consecutive lines of prior anti-lymphoma therapy[b]	104 (75)
Refractory to the last line of systemic antineoplastic therapy[b]	114 (82)
Refractory to prior anti-CD20 therapy	117 (84)
Refractory to CAR-T	39 (28)
[a]A patient is considered to be primary refractory if the patient is refractory to frontline anti-lymphoma therapy.	

[b]A patient is considered to be refractory if the patient either experiences disease progression during therapy or disease progression within < 6 months after therapy completion. A patient is considered relapsed if the patient had recurred disease ≥ 6 months after therapy completion.
[c]Per Ann Arbor Staging.
[d]Post hoc central lab FISH analysis was performed on available diagnostic baseline tumour tissue sections from 88 DLBCL patients.

The primary efficacy endpoint was overall response rate (ORR) determined by Lugano criteria (2014) as assessed by Independent Review Committee (IRC). The median follow-up time was 10.7 months (range: 0.3 to 17.9 months). The median duration of exposure was 4.1 months (range: 0 to 18 months).

Table 8 Efficacy results in study GCT3013-01 in patients with DLBCL[a]

Endpoint **IRC assessment**	**Epcoritamab** **(N=139)**
ORR[b], n (%)	86 (62)
(95% CI)	(53.3, 70)
CR[b], n (%)	54 (39)
(95% CI)	(30.7, 47.5)
PR, n (%)	32 (23)
(95% CI)	(16.3, 30.9)
DOR[b]	
Median (95% CI), months	15.5 (9.7, NR)
DOCR[b]	
Median (95% CI), months	NR (12.0, NR)
TTR, median (range), months	1.4 (1, 8.4)
CI = confidence interval; CR = complete response; DOR = duration of response; DOCR = duration of complete response; IRC = independent review committee; ORR = overall response rate; PR = partial response; TTR = time to response [a]Determined by Lugano criteria (2014) as assessed by independent review committee (IRC) [b]Included patients with initial PD by Lugano or IR by LYRIC who later obtained PR/CR.	

The median time to CR was 2.6 months (range: 1.2 to 10.2 months).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with epcoritamab in one or more subsets of the paediatric population in the treatment of mature B-cell malignancies, as per paediatric investigation plan (PIP) decision, for the granted indication (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

The population pharmacokinetics following subcutaneous administration of epcoritamab was described by a two-compartment model with first order subcutaneous absorption and target-mediated drug

elimination. The moderate to high pharmacokinetic variability for epcoritamab was observed and characterised by inter-individual variability (IIV) ranging from 25.7% to 137.5% coefficient of variation (CV) for epcoritamab PK parameters.

Based on individually estimated exposures using population pharmacokinetic modelling, following the recommended SC dose of epcoritamab 48 mg, the geometric mean (% CV) C_{max} of epcoritamab is 10.8 mcg/ml (41.7%) and AUC0-7d is 68.9 day*mcg/ml (45.1%) at the end of the weekly dosing schedule. The C_{trough} at Week 12 is 8.4 (53.3%) mcg/ml.

The geometric mean (% CV) C_{max} of epcoritamab is 7.52 mcg/ml (41.1%) and AUC0-14d is 82.6 day*mcg/ml (49.3%) at the end of q2w schedule. The C_{trough} for q2W schedule is 4.1 (73.9%) mcg/ml.

The geometric mean (% CV) C_{max} of epcoritamab is 4.76 mcg/ml (51.6%) and AUC0-28d is 74.3 day*mcg/ml (69.5%) at steady state during the q4w schedule. The C_{trough} for q4W schedule is 1.2 (130%) mcg/ml.

Absorption

The peak concentrations occurred around 3-4 days (T_{max}) in patients with LBCL receiving the 48 mg full dose.

Distribution

The geometric mean (% CV) central volume of distribution is 8.27 l (27.5%) and apparent steady-state volume of distribution is 25.6 l (81.8%) based on population PK modelling.

Biotransformation

The metabolic pathway of epcoritamab has not been directly studied. Like other protein therapeutics, epcoritamab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

Epcoritamab is expected to undergo saturable target mediated clearance. The geometric mean (% CV) clearance (l/day) is 0.441 (27.8%). The half-life of epcoritamab is concentration dependent. The population PK model-derived geometric mean half-life of full dose epcoritamab (48 mg) ranged from 22 to 25 days based on frequency of dosing.

Special populations

No clinically important effects on the pharmacokinetics of epcoritamab (Cycle 1 AUC within approximately 36%) were observed based on age (20 to 89 years), sex, or race/ethnicity (white, Asian, and other), mild to moderate renal impairment creatinine clearance (CLcr ≥ 30 ml/min to CLcr < 90 ml/min), and mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST) after accounting for differences in bodyweight. No patients with severe to end-stage renal disease (CLcr < 30 ml/min) or severe hepatic impairment (total bilirubin > 3 times ULN and any AST) have been studied. There is very limited data in moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN and any AST, N=1). Therefore, the pharmacokinetics of epcoritamab is unknown in these populations.

Like other therapeutic proteins, body weight (39 to 144 kg) has a statistically significant effect on the pharmacokinetics of epcoritamab. Based on exposure-response analysis and clinical data, considering the exposures in patients at either low body weight (e.g., 46 kg) or high body weight (e.g., 105 kg) and across body weight categories (< 65 kg, 65-< 85, ≥ 85), the effect on exposures is not clinically relevant.

Paediatric population

The pharmacokinetics of epcoritamab in paediatric patients has not been established.

5.3 Preclinical safety data

Animal pharmacology and/or toxicology

No reproductive or developmental toxicity studies in animals have been conducted with epcoritamab. Effects generally consistent with the pharmacologic mechanism of action of epcoritamab were observed in cynomolgus monkeys. These findings included dose-related adverse clinical signs (including vomiting, decreased activity, and mortality at high doses) and cytokine release, reversible hematologic alterations, reversible B-cell depletion in peripheral blood, and reversible decreased lymphoid cellularity in secondary lymphoid tissues.

Mutagenicity

Mutagenicity studies have not been conducted with epcoritamab.

Carcinogenicity

Carcinogenicity studies have not been conducted with epcoritamab.

Impairment of fertility

Animal fertility studies have not been conducted with epcoritamab, however, epcoritamab did not cause toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses up to 1 mg/kg/week in intravenous general toxicity study of 5-week duration. The AUC exposures (time-averaged over 7 days) at the high dose in cynomolgus monkeys were similar to those in patients (AUC0-7d) receiving the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products and/or diluents except those listed in section 6.6.

6.3 Shelf life

Unopened vial

2 years.

Prepared epcoritamab

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C including up to 12 hours at room temperature (20-25 °C).

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

Minimise exposure to daylight. Allow epcoritamab solution to equilibrate to room temperature before administration. Discard unused epcoritamab solution beyond the allowable storage time.

6.4 Special precautions for storage

Store and transport refrigerated (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 reconstitution/first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a bromobutyl rubber stopper coated with fluoropolymer at the contact site and aluminium seal with a plastic orange flip off cap, containing 48 mg per 0.8 ml solution for injection.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Epcoritamab must be prepared and administered by a healthcare provider as a subcutaneous injection.
Each vial of epcoritamab is intended for single use only.

Each vial contains an overfill that allows withdrawal of the labelled amount.

The administration of epcoritamab takes place over the course of 28-day cycles, following the dosing schedule in section 4.2.

Epcoritamab should be inspected visually for particulate matter and discolouration prior to administration. The solution for injection should be a colourless to slightly yellow solution. Do not use if the solution is discoloured, or cloudy, or if foreign particles are present.

48 mg full dose preparation instructions - **No dilution required**
Tepkinly 48 mg vial is supplied as ready-to-use solution that does not need dilution prior to administration.
Epcoritamab has to be prepared using aseptic technique. Filtration of the solution is not required.

1) Prepare epcoritamab vial a) Retrieve one 48 mg epcoritamab vial with the **orange** cap from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour. c) Gently swirl the epcoritamab vial. **DO NOT** vortex or vigorously shake the vial.
2) Withdraw dose Withdraw **0.8 ml of epcoritamab** into a syringe.
3) Label syringe Label the syringe with the product name, dose strength (48 mg), date and the time of day. For storage of the prepared epcoritamab, see section 6.3.
4) Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/23/1759/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

Rentschler Biopharma Inc.
27 Maple Street
Milford, MA 01757
USA

Name and address of the manufacturer responsible for batch release

AbbVie S.r.l.
S.R. 148 Pontina, km 52 SNC
04011 Campoverde di Aprilia (LT)
ITALY

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**

Additional risk minimisation measures to minimise the important identified risks of CRS and ICANS consist of a Patient Card targeted to patients treated with epcoritamab.

Prior to the launch of epcoritamab in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the patient card, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The Marketing Authorisation Holder (MAH) shall ensure that in each Member State where epcoritamab is marketed, HCPs who are expected to prescribe epcoritamab and patients treated with epcoritamab have access to/are provided with the Patient Card which will inform and explain to patients the risks of CRS and ICANS.

The Patient Card will contain the following key messages:

- Provide information on signs/symptoms of CRS and ICANS
- Alert patients to promptly contact their HCPs/emergency care if they observe any of the signs or symptoms of CRS and ICANS
- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using epcoritamab.
- Contact details of the epcoritamab prescriber

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PAES: The MAH shall provide the updated CSR for the escalation part of study GCT3013-01.	22 Dec 2023

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
In order to confirm the safety and efficacy of epcoritamab in the treatment of R/R DLBCL after two or more lines of systemic therapy, the primary (including final OS analysis) and final CSR for study GCT3013-05 should be submitted. - Primary analysis CSR (including final OS analysis) – due date: Q4/2024 - Final CSR – due data: Q1 2029.	 Q4/2024 Q1/2029
In order to confirm the safety and efficacy of epcoritamab in the treatment of relapsed or refractory DLBCL after two or more lines of systemic therapy, the MAH should submit the final CSR for the pivotal aNHL cohort of study GCT3013-01.	Q3/2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tepkinly 4 mg/0.8 ml concentrate for solution for injection
epcoritamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 4 mg of epcoritamab in 0.8 ml, at a concentration of 5 mg/ml.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate, acetic acid, sorbitol (E420), polysorbate 80, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for injection

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

For single use only.

Dilute prior to use.

Read the package leaflet before use.

Open here

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1759/001

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 LABEL

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

Tepkinly 4 mg/0.8 ml sterile concentrate
epcoritamab
SC after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

AbbVie (as logo)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tepkinly 48 mg solution for injection
epcoritamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 48 mg of epcoritamab in 0.8 ml, at a concentration of 60 mg/ml.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate, acetic acid, sorbitol (E420), polysorbate 80, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

For single use only.

Read the package leaflet before use.

Open here

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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1759/002

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 LABEL

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

Tepkinly 48 mg injection
epcoritamab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.8 ml

6. OTHER

AbbVie (as logo)

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tepkinly 4 mg/0.8 ml concentrate for solution for injection
epcoritamab

▼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 start using 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tepkinly is and what it is used for

What Tepkinly is

Tepkinly is a cancer medicine that contains the active substance epcoritamab. Tepkinly is used on its own (monotherapy) to treat adult patients who have a blood cancer called diffuse large B-cell lymphoma (DLBCL) when the disease has come back or did not respond to previous treatment after at least two prior therapies.

How Tepkinly works

Epcoritamab is specifically designed to help your own immune system to attack cancer (lymphoma) cells. Epcoritamab acts by attaching to your body's immune cells and cancer cells, bringing them together, so that your immune system can destroy the cancer cells.

2. What you need to know before you use Tepkinly

Do not use Tepkinly

If you are allergic to epcoritamab or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor or nurse before you are given Tepkinly.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Tepkinly if you
- have current or past problems with your nervous system – such as seizures

- have an infection
- are due to have a vaccine or you know you may need to have one in the near future.

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

Tell your doctor straight away if you get symptoms of any of the side effects listed below, during or after treatment with Tepkinly. You may need additional medical treatment.

- **Cytokine release syndrome –** a life-threatening condition causing fever, vomiting, difficulty breathing/shortness of breath, chills, rapid heartbeat, headache and dizziness or light-headedness associated with medicines that stimulate T cells.
  - Before each injection under the skin, you may be given medicines which help reduce possible effects of cytokine release syndrome.
- **ICANS (immune effector cell-associated neurotoxicity syndrome)**- Symptoms may include problems with use of language (including speech, understanding, writing and reading), drowsiness, confusion/disorientation, muscle weakness, seizures, swelling of a part of the brain, and memory loss.
- **Tumour lysis syndrome –** some people may get unusual levels of some salts in the blood – caused by the fast breakdown of cancer cells during treatment. This is called tumour lysis syndrome (TLS).
  - Your doctor or nurse will do blood tests to check for this condition. Before each injection under the skin, you should be well-hydrated and may be given other medicines that can help reduce high levels of uric acid and help reduce possible effects of tumour lysis syndrome.
- **Tumour flare –** as your cancer is destroyed, it may react and appear to get worse – this is called 'tumour flare reaction'.
- **Infections** – you may get signs of infection, such as fever of 38 °C or above, chills, cough, or pain with urination which can vary depending on where in the body the infection is.

Children and adolescents

Tepkinly is not recommended in children and adolescents under 18 years, as there is no information about use in this age group.

Other medicines and Tepkinly

Tell your doctor or pharmacist if you are taking or using, have recently taken or used, or might take or use any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use Tepkinly during pregnancy, as it may affect your unborn baby. Your doctor may ask you to take a pregnancy test before starting treatment.

Contraception

If you are a woman who is able to have children, you must use effective contraception to avoid becoming pregnant while taking Tepkinly and for at least 4 months after your last dose of Tepkinly. If you become pregnant during this time, you must talk to your doctor straight away.

Talk to your doctor or nurse about suitable methods of contraception.

Breast-feeding

You must not breast-feed during treatment with Tepkinly and for at least 4 months after the last dose. It is not known whether Tepkinly passes into breast milk and whether it could affect your baby.

Fertility

The effect of Tepkinly on male and female fertility is unknown.

Driving and using machines

Due to the possible symptoms of ICANS, you should be careful while driving, cycling or using heavy or potentially dangerous machines. If you currently have such symptoms, avoid these activities and contact your doctor, nurse, or pharmacist. See section 4 for more information about side effects.

Tepkinly contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Tepkinly contains sorbitol

This medicine contains 21.9 mg sorbitol in each vial, which is equivalent to 27.33 mg/ml.

3. How Tepkinly will be given

A doctor experienced in treating cancer will take care of your treatment. Follow the treatment schedule explained to you by your doctor.

Tepkinly will be given to you by a doctor or nurse as an injection under your skin.
Tepkinly will be given to you in cycles of 28 days, on a dosing schedule given to you by your doctor.

You will be given Tepkinly according to the following schedule

Cycle	**Dosing schedule**
Cycles 1 to 3	Weekly
Cycles 4 to 9	Every two weeks
Cycles 10 and beyond	Every four weeks

You may be given other medicines before you are given Tepkinly. This is to help prevent reactions such as cytokine release syndrome and fever in Cycle 1 (and potentially future cycles).
These medicines may include

- Corticosteroids – such as prednisolone or equivalent
- An antihistamine – such as diphenhydramine
- Paracetamol

The first full dose (48 mg) of Tepkinly will be given to you on Cycle 1 Day 15. Your doctor will monitor how your treatment is working and ask you to stay in a hospital for 24 hours after the first full dose (48 mg) because this is when reactions such as CRS, ICANS and fever are most likely to happen.

You will be given Tepkinly for as long as your doctor thinks you are benefitting from the treatment.

Your doctor may delay or completely stop your treatment with Tepkinly if you have certain side effects.

If you forget to use Tepkinly
If you forget or miss your medical appointment, make another one straight away. For the treatment to be fully effective, it is very important not to miss a dose.

If you stop using Tepkinly
Do not stop treatment with Tepkinly unless you have discussed this with your doctor. 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, pharmacist 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 notice any of the symptoms of the following serious side effects. You may only get one or some of these symptoms.

Cytokine release syndrome (CRS) (Very common: may affect more than 1 in 10 people)
Symptoms can include

- fever
- vomiting
- dizziness or light-headedness
- chills
- fast heartbeat
- difficulty breathing/shortness of breath
- headache

Immune effector cell-associated neurotoxicity syndrome (ICANS) (Common: may affect up to 1 in 10 people)

- effects on your nervous system, the symptoms of which can occur days or weeks after you receive the injection, may initially be subtle. Some of these symptoms may be signs of a serious immune reaction called "immune effector cell-associated neurotoxicity syndrome" (ICANS). Symptoms can include
  - difficulty speaking or writing
  - drowsiness
  - confusion/disorientation
  - muscle weakness
  - seizures
  - memory loss

Tumour lysis syndrome (TLS) (**Common:** may affect up to 1 in 10 people)
Symptoms can include

- fever
- chills
- vomiting
- confusion
- shortness of breath
- seizures
- irregular heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle or joint pain

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

- viral infection
- pneumonia (lung infection)
- decreased hunger
- irregular heartbeat
- pain in bones, joints, ligaments and muscles
- pain in the belly area
- headache
- nausea
- diarrhoea
- vomiting
- tiredness
- injection site reactions
- fever
- swelling

Shown in blood tests

- low levels of a type of white blood cells that fight infection (neutropenia)
- low levels of red blood cells, which can cause tiredness, pale skin, and shortness of breath (anaemia)
- low levels of blood platelets, which can lead to bleeding and bruising (thrombocytopenia)

Common: may affect up to 1 in 10 people

- fever due to infection when you have low levels of white blood cells (febrile neutropenia)
- upper respiratory tract infections (infection of the airways)
- tender swollen lymph nodes, chest pain, cough or difficulty breathing, pain at the site of the tumour (tumour flare)
- fungal infections (caused by a type of germ called a fungus)
- skin infections
- life-threatening reaction the body has to an infection (sepsis)
- decrease in a type of white blood cell called a lymphocyte, that may affect the body's ability to fight infection (lymphopenia)
- a rapid breakdown of tumour cells resulting in chemical changes in the blood and damage to organs, including the kidneys, heart, and liver (tumour lysis syndrome)
- extra fluid around the lungs that can make it difficult to breathe (pleural effusion)
- rash
- itching (pruritus)

Shown in blood tests

- low level of phosphates in the blood, potassium, magnesium or sodium
- increased blood level of creatinine, a breakdown product from muscle tissue
- increased blood level of liver proteins, which may show problems with the liver

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Tepkinly

Tepkinly will be stored by the doctor, nurse, or pharmacist at the hospital or clinic. To correctly store Tepkinly

- 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 vial label and carton after EXP. The expiry date refers to the last day of that month.
- Store and transport refrigerated (2 °C to 8 °C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Tepkinly 4 mg/0.8 ml is a concentrated solution and must be diluted prior to use.
- If not used immediately, the prepared solution may be stored for up to 24 hours at 2 °C to 8 °C from the time of preparation.
- Within these 24 hours, the prepared solution can be stored for up to 12 hours at room temperature (20 °C - 25 °C) from the start of dose preparation to administration.
- Allow the dilution solution to warm to room temperature before using.

Your doctor, nurse or pharmacist will throw away any unused medicine following local requirements. These measures will help protect the environment.

6. Contents of the pack and other information

What Tepkinly contains
- The active substance is epcoritamab. Each 0.8 ml vial contains 4 mg of epcoritamab at a concentration of 5 mg/ml.
- The other excipients are sodium acetate trihydrate, acetic acid, sorbitol (E420), polysorbate 80, water for injections (see section 2 “Tepkinly contains sodium” and “Tepkinly contains sorbitol”).

What Tepkinly looks like and contents of the pack

Tepkinly is a concentrate for solution for injection. It is a colourless to slightly yellow solution provided in a glass vial.

Each carton contains 1 vial.

Marketing Authorisation Holder

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

Manufacturer

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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. There are also links to other websites about rare diseases and treatments.

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This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Epcoritamab is prepared and administered as a subcutaneous injection.
Each vial of epcoritamab is intended for single use only.

Each vial contains an overfill that allows withdrawal of the labelled amount.

Epcoritamab must be diluted and administered by a healthcare professional using aseptic technique. Filtration of the diluted solution is not required.

Epcoritamab should be inspected visually for particulate matter and discolouration prior to administration. The concentrate should be a colourless to slightly yellow solution. Do not use if the solution is discoloured, or cloudy, or if foreign particles are present.

0.16 mg priming dose preparation instructions – **2 dilutions required**
Use an appropriately sized, syringe, vial and needle for each transfer step.
1) Prepare Tepkinly vial
    a) Retrieve one 4 mg/0.8 ml Tepkinly vial with the **light blue** cap from the refrigerator.
    b) Allow the vial to come to room temperature for no more than 1 hour.
    c) Gently swirl the Tepkinly vial.

DO NOT vortex or vigorously shake the vial.

2) Perform first dilution
    a) Label an appropriately sized empty vial as "**dilution A**".
    b) Transfer **0.8 ml of Tepkinly** into the **dilution A** vial.
    c) Transfer **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** vial. The initial diluted solution contains 0.8 mg/ml of epcoritamab.
    d) Gently swirl the **dilution A** vial for 30 – 45 seconds.

3) Perform second dilution
    a) Label an appropriately sized empty vial as **"dilution B"**.
    b) Transfer **2 ml of solution** from the **dilution A** vial into the **dilution B** vial. The **dilution A** vial is no longer needed and should be discarded.
    c) Transfer **8 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution B** vial to make a final concentration of 0.16 mg/ml.
    d) Gently swirl the **dilution B** vial for 30 – 45 seconds.

4) Withdraw dose
    Withdraw **1 ml of the diluted epcoritamab** from the **dilution B** vial into a syringe. The **dilution B** vial is no longer needed and should be discarded.

5) Label syringe

Label the syringe with the product name, dose strength (0.16 mg), date and the time of day.

6) Discard the vial and any unused portion of Tepkinly in accordance with local requirements.

0.8 mg intermediate dose preparation instructions – **1 dilution required**

Use an appropriately sized, syringe, vial and needle for each transfer step.

1) Prepare Tepkinly vial

a) Retrieve one 4 mg/0.8 ml Tepkinly vial with the **light blue** cap from the refrigerator.

b) Allow the vial to come to room temperature for no more than 1 hour.

b) Gently swirl the Tepkinly vial.

DO NOT vortex or vigorously shake the vial.

2) Perform dilution

a) Label an appropriately sized empty vial as **"dilution A"**.

b) Transfer **0.8 ml of Tepkinly** into the **dilution A** vial.

c) Transfer **4.2 ml of sodium chloride 9 mg/ml (0.9%) sterile solution** into the **dilution A** vial to make a final concentration of 0.8 mg/ml.

d) Gently swirl the **dilution A** vial for 30 – 45 seconds.

3) Withdraw dose

Withdraw **1 ml of the diluted epcoritamab** from the **dilution A** vial into a syringe. The **dilution A** vial is no longer needed and should be discarded.

4) Label syringe

Label the syringe with the product name, dose strength (0.8 mg), date and the time of day.

5) Discard the vial and any unused portion of Tepkinly in accordance with local requirements.

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.

Package leaflet: Information for the patient

Tepkinly 48 mg solution for injection
epcoritamab

▼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 start using 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tepkinly is and what it is used for

What Tepkinly is

Tepkinly is a cancer medicine that contains the active substance epcoritamab. Tepkinly is used on its own (monotherapy) to treat adult patients who have a blood cancer called diffuse large B-cell lymphoma (DLBCL) when the disease has come back or did not respond to previous treatment after at least two prior therapies.

How Tepkinly works

Epcoritamab is specifically designed to help your own immune system to attack cancer (lymphoma) cells. Epcoritamab acts by attaching to your body's immune cells and cancer cells, bringing them together, so that your immune system can destroy the cancer cells.

2. What you need to know before you use Tepkinly

Do not use Tepkinly

If you are allergic to epcoritamab or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor or nurse before you are given Tepkinly.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Tepkinly if you
- have current or past problems with your nervous system – such as seizures
- have an infection

- are due to have a vaccine or you know you may need to have one in the near future.

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

Tell your doctor straight away if you get symptoms of any of the side effects listed below, during or after treatment with Tepkinly. You may need additional medical treatment.

- **Cytokine release syndrome –** a life-threatening condition causing fever, vomiting, difficulty breathing/shortness of breath, chills, rapid heartbeat, headache and dizziness or light-headedness associated with medicines that stimulate T cells.
  − Before each injection under the skin, you may be given medicines which help reduce possible effects of cytokine release syndrome.
- **ICANS (immune effector cell-associated neurotoxicity syndrome)**- Symptoms may include problems with use of language (including speech, understanding, writing and reading), drowsiness, confusion/disorientation, muscle weakness, seizures, swelling of a part of the brain, and memory loss.
- **Tumour lysis syndrome –** some people may get unusual levels of some salts in the blood – caused by the fast breakdown of cancer cells during treatment. This is called tumour lysis syndrome (TLS).
  - Your doctor or nurse will do blood tests to check for this condition. Before each injection under the skin, you should be well-hydrated and may be given other medicines that can help reduce high levels of uric acid and help reduce possible effects of tumour lysis syndrome.
- **Tumour flare –** as your cancer is destroyed, it may react and appear to get worse – this is called 'tumour flare reaction'.
- **Infections** – you may get signs of infection, such as fever of 38 °C or above, chills, cough, or pain with urination which can vary depending on where in the body the infection is.

Children and adolescents

Tepkinly is not recommended in children and adolescents under 18 years, as there is no information about use in this age group.

Other medicines and Tepkinly

Tell your doctor or pharmacist if you are taking or using, have recently taken or used, or might take or use any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use Tepkinly during pregnancy, as it may affect your unborn baby. Your doctor may ask you to take a pregnancy test before starting treatment.

Contraception

If you are a woman who is able to have children, you must use effective contraception to avoid becoming pregnant while taking Tepkinly and for at least 4 months after your last dose of Tepkinly. If you become pregnant during this time, you must talk to your doctor straight away.

Talk to your doctor or nurse about suitable methods of contraception.

Breast-feeding

You must not breast-feed during treatment with Tepkinly and for at least 4 months after the last dose. It is not known whether Tepkinly passes into breast milk and whether it could affect your baby.

Fertility

The effect of Tepkinly on male and female fertility is unknown.

Driving and using machines

Due to the possible symptoms of ICANS, you should be careful while driving, cycling or using heavy or potentially dangerous machines. If you currently have such symptoms, avoid these activities and contact your doctor, nurse, or pharmacist. See section 4 for more information about side effects.

Tepkinly contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Tepkinly contains sorbitol

This medicine contains 21.9 mg sorbitol in each vial, which is equivalent to 27.33 mg/ml.

3. How Tepkinly will be given

A doctor experienced in treating cancer will take care of your treatment. Follow the treatment schedule explained to you by your doctor.

Tepkinly will be given to you by a doctor or nurse as an injection under your skin.
Tepkinly will be given to you in cycles of 28 days, on a dosing schedule given to you by your doctor.

You will be given Tepkinly according to the following schedule

Cycle	**Dosing schedule**
Cycles 1 to 3	Weekly
Cycles 4 to 9	Every two weeks
Cycles 10 and beyond	Every four weeks

You may be given other medicines before you are given Tepkinly. This is to help prevent reactions such as cytokine release syndrome and fever in Cycle 1 (and potentially future cycles).
These medicines may include

- Corticosteroids – such as prednisolone or equivalent
- An antihistamine – such as diphenhydramine
- Paracetamol

The first full dose (48 mg) of Tepkinly will be given to you on Cycle 1 Day 15. Your doctor will monitor how your treatment is working and ask you to stay in a hospital for 24 hours after the first full dose (48 mg) because this is when reactions such as CRS, ICANS and fever are most likely to happen.

You will be given Tepkinly for as long as your doctor thinks you are benefitting from the treatment.

Your doctor may delay or completely stop your treatment with Tepkinly if you have certain side effects.

If you forget to use Tepkinly
If you forget or miss your medical appointment, make another one straight away. For the treatment to be fully effective, it is very important not to miss a dose.

If you stop using Tepkinly
Do not stop treatment with Tepkinly unless you have discussed this with your doctor. 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, pharmacist 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 notice any of the symptoms of the following serious side effects. You may only get one or some of these symptoms.

Cytokine release syndrome (CRS) (Very common: may affect more than 1 in 10 people)
Symptoms can include

- fever
- vomiting
- dizziness or light-headedness
- chills
- fast heartbeat
- difficulty breathing/shortness of breath
- headache

Immune effector cell-associated neurotoxicity syndrome (ICANS) (Common: may affect up to 1 in 10 people)

- effects on your nervous system, the symptoms of which can occur days or weeks after you receive the injection, may initially be subtle. Some of these symptoms may be signs of a serious immune reaction called "immune effector cell-associated neurotoxicity syndrome" (ICANS). Symptoms can include
  - difficulty speaking or writing
  - drowsiness
  - confusion/disorientation
  - muscle weakness
  - seizures
  - memory loss

Tumour lysis syndrome (TLS) (**Common:** may affect up to 1 in 10 people)
Symptoms can include

- fever
- chills
- vomiting
- confusion
- shortness of breath
- seizures
- irregular heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle or joint pain

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

- viral infection

- pneumonia (lung infection)
- decreased hunger
- irregular heartbeat
- pain in bones, joints, ligaments and muscles
- pain in the belly area
- headache
- nausea
- diarrhoea
- vomiting
- tiredness
- injection site reactions
- fever
- swelling

Shown in blood tests
- low levels of a type of white blood cells that fight infection (neutropenia)
- low levels of red blood cells, which can cause tiredness, pale skin, and shortness of breath (anaemia)
- low levels of blood platelets, which can lead to bleeding and bruising (thrombocytopenia)

Common: may affect up to 1 in 10 people
- fever due to infection when you have low levels of white blood cells (febrile neutropenia)
- upper respiratory tract infections (infection of the airways)
- tender swollen lymph nodes, chest pain, cough or difficulty breathing, pain at the site of the tumour (tumour flare)
- fungal infections (caused by a type of germ called a fungus)
- skin infections
- life-threatening reaction the body has to an infection (sepsis)
- decrease in a type of white blood cell called a lymphocyte, that may affect the body's ability to fight infection (lymphopenia)
- a rapid breakdown of tumour cells resulting in chemical changes in the blood and damage to organs, including the kidneys, heart, and liver (tumour lysis syndrome)
- extra fluid around the lungs that can make it difficult to breathe (pleural effusion)
- rash
- itching (pruritus)

Shown in blood tests
- low level of phosphates in the blood, potassium, magnesium or sodium
- increased blood level of creatinine, a breakdown product from muscle tissue
- increased blood level of liver proteins, which may show problems with the liver

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Tepkinly

Tepkinly will be stored by the doctor, nurse, or pharmacist at the hospital or clinic. To correctly store Tepkinly
- 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 vial label and carton after EXP. The expiry date refers to the last day of that month.

- Store and transport refrigerated (2 °C to 8 °C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
-
- If not used immediately, the prepared solution may be stored for up to 24 hours at 2 °C to 8 °C from the time of preparation.
- Within these 24 hours, the prepared solution can be stored for up to 12 hours at room temperature (20 °C-25 °C) from the start of dose preparation to administration.
- Allow the solution to warm to room temperature before using.

Your doctor, nurse or pharmacist will throw away any unused medicine following local requirements. These measures will help protect the environment.

6. Contents of the pack and other information

What Tepkinly contains
- The active substance is epcoritamab. Each 0.8 ml vial contains 48 mg of epcoritamab at a concentration of 60 mg/ml.
- The other excipients are sodium acetate trihydrate, acetic acid, sorbitol (E420), polysorbate 80, water for injections (see section 2 “Tepkinly contains sodium” and “Tepkinly contains sorbitol”).

What Tepkinly looks like and contents of the pack

Tepkinly is a solution for injection. It is a colourless to slightly yellow solution provided in a glass vial.

Each carton contains 1 vial.

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The following information is intended for healthcare professionals only:

Epcoritamab is prepared and administered as a subcutaneous injection.
Each vial of epcoritamab is intended for single use only.

Each vial contains an overfill that allows withdrawal of the labelled amount.

Epcoritamab must be prepared and administered by a healthcare professional using aseptic technique - **No dilution required**.

Tepkinly 48 mg vial is supplied as ready-to-use solution that does not need dilution prior to administration. Filtration of the solution is not required.

Epcoritamab should be inspected visually for particulate matter and discolouration prior to administration. The solution for injection should be a colourless to slightly yellow solution. Do not use if the solution is discoloured, or cloudy, or if foreign particles are present.

1) Prepare Tepkinly vial a) Retrieve one 48 mg Tepkinly vial with the **orange** cap from the refrigerator. b) Allow the vial to come to room temperature for no more than 1 hour. c) Gently swirl the Tepkinly vial. **DO NOT** vortex or vigorously shake the vial.
2) Withdraw dose Withdraw 0.8 ml of Tepkinly into a syringe.
3) Label syringe Label the syringe with the product name, dose strength (48 mg), date and the time of day.
4) Discard the vial and any unused portion of Tepkinly in accordance with local requirements.

Storage for prepared Tepkinly

- Use immediately or store Tepkinly solution in a refrigerator and protect from light for up to 24 hours at 2 °C to 8 °C from the time of preparation.
- Within these 24 hours, Tepkinly solution can be stored for up to 12 hours at room temperature from the start of dose preparation to administration.
- Minimise exposure to daylight.
- Allow Tepkinly solution to equilibrate to room temperature before administration.
- Discard unused Tepkinly solution beyond the allowable storage time.

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.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.