swissmedic

Date: 30 September 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Tepkinly

International non-proprietary name: epcoritamab

Pharmaceutical form:	solution for injection
Dosage strength(s):	4 mg/0.8 ml
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	AbbVie AG
Marketing authorisation no.:	69161
Decision and decision date:	extension of therapeutic indication as a temporary authorisation in accordance with Art. 9a TPA approved on 19 August 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
CAR-T cell	Chimeric antigen receptor T cell
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CRS	Cytokine release syndrome
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FL	Follicular lymphoma
IC/EC_{50}	Half-maximal inhibitory/effective concentration
Ig	Immunoglobulin
INN	International non-proprietary name
IRC	Independent review committee
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 10 November 2022.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9*a* TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Tepkinly is indicated as monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

2.2.2 Approved indication

Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy, including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide (see "Clinical efficacy" section).
The results on the effectiveness and safety of Tepkinly in patients with previous anti-CD19-targeted CAR-T cell therapy are limited (see "Warnings and precautions" section).

2.2.3 Requested dosage

Summary of the requested standard dosage:
Cycles of 28 days each.
3-step step-up dose schedule for patients with follicular lymphoma

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	3 mg (step-up dose 3)
		22	48 mg (first full dose)
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, 3 mg is a second intermediate dose, and 48 mg is a full dose.			

Tepkinly should be administered until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	24 April 2025
Formal control completed	28 April 2025
Preliminary decision	1 July 2025
Response to preliminary decision	30 July 2025
Final decision	19 August 2025
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

In accordance with Art. 13 TPA, Swissmedic has only assessed parts of the primary data submitted with this application and relies on the assessment of the foreign reference authority EMA. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority EMA. This SwissPAR relates to the assessment report Tepkinly Procedure No. EMEA/H/C/005985/II/0001 (published 18 October 2024) issued by EMA. Swissmedic focused its evaluation on the patient population included in the submitted pivotal study GCT3013-01.

3 Medical context

Follicular lymphoma (FL) is the most common indolent non-Hodgkin's lymphoma and the second most common lymphoma in Europe[1]. Patients with refractory or relapsing FL after ≥ 2 prior lines of therapy, including anti-CD20 and chemotherapeutic regimens, have a poor prognosis. Progression-free survival (PFS) and overall survival (OS) shorten with each subsequent relapse and line of therapy, with median PFS ranges of 1 - 1.1 years for third-line patients and median OS of 4.8-8.8 years[2,3].

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority (EMA). The nonclinical aspects in this SwissPAR refer to the publicly available assessment report (Extension of indication variation assessment report – Tepkinly, 27 June 2024, EMA/CHMP/369446/2024) issued by EMA.

[1] Mounier et al. Lancet Haematol. 2015 Nov; 2(11):481-91
[2] Rivas-Delgado et al. Br J Haematol 2019 Mar;184(5):753-759
[3] Batlevi et al. Blood Cancer J. 2020 Jul 17;10(7):7

5 Clinical aspects

5.1 Efficacy

The applicant submitted one pivotal single-arm study with multiple cohorts (GCT3013-01) for the evaluation of the efficacy and safety of epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (R/R FL) with ≥ 2 prior lines of systemic therapy, including previous therapy with an anti-CD20 antibody and either an alkylating agent or lenalidomide. The expansion cohort of patients with indolent non-Hodgkin's lymphoma included patients with FL. The optimisation cohort was provided as supportive evidence. For details of study design, please refer to the "Clinical efficacy" section of the attached Information for healthcare professionals.

The primary endpoint of the expansion cohort was overall response rate (ORR) assessed by an independent review committee (IRC).

In total, 128 patients with FL were included in the expansion cohort. The median age was 65 years and 62% were male. The median number of prior therapies was 3 (range 2-9). Overall, 37% of patients had 2 prior lines of systemic therapies, 32% 3 prior lines of therapy and 31% ≥ 4 prior lines of systemic therapy. Most patients were refractory to therapy with an anti-CD20 antibody (79%) and 70% of patients were refractory to an anti-CD20 antibody and alkylating agent.

Overall, 12 patients in the GCT3013-01 study had prior exposure to CAR-T cell therapy. For details of the included study population, please refer to the "Clinical efficacy" section of the attached Information for healthcare professionals.

The ORR (IRC) was 83% and the median duration of response (DOR) was 21.4 months.

5.2 Safety

The evaluation of safety focused on the evaluation of the relevant safety risk of cytokine release syndrome (CRS). The Information for healthcare professionals was adapted accordingly. For details of the safety and management of CRS, please refer to the attached Information for healthcare professionals.

5.3 Final clinical benefit-risk assessment

The benefit-risk assessment is positive for temporary authorisation of epcoritamab in patients with relapsed or refractory FL. However, the indication was adapted according to the included patient population, who received at least 2 prior lines of systemic therapy, including a monoclonal anti-CD20 antibody and either an alkylating agent or lenalidomide. In addition, the efficacy and safety data in patients with prior anti-CD19 CAR-T cell therapy is limited.
Since confirmation of clinical benefit is a condition of temporary authorisation, the applicant will submit updated results from the expansion and optimisation cohort of study GTC 3013-01, interim analysis results (IA2) and final analysis of the confirmatory study M20-638.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Tepkinly was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Tepkinly has been authorised temporarily, see “Indications/Uses” section.

TEPKINLY® 4 mg/0,8 ml, solution for injection

Composition

Active substances

Epcoritamab (produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology).

Excipients

Sodium acetate trihydrate (corresponds to 0,48 mg sodium), acetic acid, sorbitol (E420) 21,84 mg, polysorbate 80, water for injection.

Pharmaceutical form and active substance quantity per unit

Solution for injection
Each vial contains 4 mg epcoritamab in 0,8 ml solution (5 mg/ml).
Colourless to slightly yellow solution, pH 5.5 and osmolality of approximately 211 mOsm/kg.

Indications/Uses

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, including a CD20 antibody, where patient is unable to receive or have previously received anti-CD19-targeted CAR-T cell therapy (see “Clinical efficacy” section).
Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy including an anti-CD20 monoclonal antibody and an alkylating agent or lenalidomide (see “Clinical efficacy” section).
The results on the effectiveness and safety of Tepkinly in patients with previous anti-CD19-targeted CAR-T cell therapy are limited (see “Warnings and precautions” section).
These indications have been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

Dosage/Administration

Tepkinly is for subcutaneous (SC) injection only. Tepkinly should only be administered under the supervision of a healthcare professional qualified in the use of anti-cancer therapies, in a setting with

appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Monitoring

Monitor patients for potential CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS) and manage per current practice guidelines following epcoritamab administration during Cycle 1 and in subsequent cycles. Counsel patients 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 “Warnings and precautions”).
Patients should be monitored within proximity of a healthcare facility (or alternatively in an inpatient setting) for signs and symptoms of CRS and/or ICANS for 24 hours during Cycle 1 Day 1 and Day 8 (DLBCL) or during Cycle 1 Day 1, Day 8, Day 15 and Day 22 (FL).
Patients with DLBCL should be hospitalized 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.
Intensive monitoring should be performed for the next administration of Tepkinly if CRS Grade 3 or clinically relevant neurological toxicities (e.g., serious or life-threatening neurological toxicities including ICANS) related to Tepkinly administration were observed during the previous administration. In these cases, inpatient monitoring should be performed for at least 72 hours and patients should be monitored daily for signs and symptoms of CRS, neurological and other toxicities for up to 7 days after administration of Tepkinly.

Posology

Recommended pre-medication and dose schedule

Administer Tepkinly according to the step-up dose schedule in 28-day cycles which is outlined in Table 1 for patients with diffuse large B-cell lymphoma and Table 2 for patients with follicular lymphoma.

Table 1: Tepkinly 2-step step-up dose schedule for patients with diffuse large B-cell lymphoma

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.			

Table 2: Tepkinly 3-step step-up dose schedule for patients with follicular lymphoma

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	3 mg (Step-up dose 3)
		22	48 mg (First full dose)
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, 3 mg is a second intermediate dose and 48 mg is a full dose .			

Tepkinly should be administered until disease progression or unacceptable toxicity.

Patients should be well hydrated before using Tepkinly.

Details on recommended premedication for cytokine release syndrome (CRS) are shown in Table 3.

Table 3: Epcoritamab premedication

Cycle	Patient requiring premedication	Premedication	Administration
Cycle 1	All patients	Dexamethasone[b] (15 mg oral or intravenous) or Prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to each weekly administration of epcoritamab • And for three consecutive days following the administration of epcoritamab in Cycle 1

		• Diphenhydramine (50 mg oral or intravenous) or equivalent • Paracetamol (650 to 1000 mg oral)	• 30-120 minutes prior to the administration of epcoritamab
Cycle 2 and beyond	Patients who experienced Grade 2 or 3[a] CRS with previous dose	Dexamethasone[b] (15 mg oral or intravenous) or Prednisolone (100 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 any grade of CRS
[a] Patients will be permanently discontinued from epcoritamab after a Grade 4 CRS event. [b] Dexamethasone is the preferred corticosteroid for CRS prophylaxis based on the GCT3013-01 Optimisation study.			

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

Tepkinly should be administered to adequately hydrated patients.
It is strongly recommended that all patients adhere to the following fluid guidelines during Cycle 1, unless medically contraindicated:

- 2-3 L of fluid intake during the 24 hours prior to each epcoritamab administration
- Hold antihypertensive medications for 24 hours prior to each epcoritamab administration
- Administer 500 ml isotonic intravenous (IV) fluids on the day of epcoritamab prior to dose administration; AND
- 2-3 L of fluid intake during the 24 hours following each epcoritamab administration.

Patients at an increased risk for clinical tumour lysis syndrome (CTLS) are recommended to receive hydration and prophylactic treatment with an uric acid lowering agent.

Dose adjustment following undesirable effects

Cytokine release syndrome (CRS)

Patients treated with epcoritamab may develop Cytokine release syndrome (CRS).
Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 4. Patients who experience CRS should be monitored more frequently during next scheduled epcoritamab administration.

Table 4: CRS grading and management guidance

Grade[a]	Presenting Symptoms	Actions
Grade 1	**Temperature ≥ 38°C[b]**	• Withhold epcoritamab and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of epcoritamab.[c]
Grade 2	**Temperature ≥ 38°C[b] with:** Hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by.	• Withhold epcoritamab and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of epcoritamab.[c] • Administer premedication[d] prior to next dose of epcoritamab. • For the next dose of epcoritamab, monitor more frequently and consider hospitalization.
Grade 3	**Temperature ≥ 38°C[b] with:** Hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	• Withhold epcoritamab and manage per current practice guidelines, which may include intensive care. • Ensure CRS symptoms are resolved prior to the next dose of epcoritamab.[c] • Administer premedication[d] prior to next dose of epcoritamab. • Hospitalize for the next dose of epcoritamab.
		Recurrent Grade 3 CRS • Permanently discontinue epcoritamab.

Grade[a]	Presenting Symptoms	Actions
		• Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.
Grade 4	**Temperature ≥ 38°C[b] with:** Hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation).	• Permanently discontinue epcoritamab. • Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.

[b] Premedication may mask fever, therefore if clinical presentation is consistent with CRS, follow these management guidelines.

[c] Refer to section "**Delayed administration**" for information on restarting Tepkinly after dosage delays (see "Dosage/Administration")

[d] If Grade 2 or 3 CRS occurs with the second full dose (48 mg) or beyond, administer CRS premedications with each subsequent dose until a Tepkinly dose is given without subsequent CRS of Grade 2 or higher. Refer to Table 2 for additional information on premedication.

[e] Low-flow oxygen defined as oxygen delivered at < 6L/minute; high-flow oxygen defined as oxygen delivered at ≥ 6 L/minute.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Monitor patients for signs and symptoms of ICANS. Rule out other causes of neurologic symptoms. If ICANS is suspected, manage according to the recommendations in Table 5.

Table 5: ICANS grading and management guidance

Grade[a]	Presenting Symptoms[b]	Actions
Grade 1	ICE score 7-9[c], Or depressed level of consciousness[d]: awakens spontaneously.	• Withhold epcoritamab until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • If an ICANS should occur, manage it according to the current practice guidelines.
Grade 2	ICE score 3-6[c], Or depressed level of consciousness[d]: awakens to voice.	• Withhold epcoritamab until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • If an ICANS should occur, manage it according to the current practice guidelines.

Grade[a]	Presenting Symptoms[b]	Actions
Grade 3	ICE score 0-2[c], Or depressed level of consciousness[d]: awakens only to tactile stimulus, Or seizures,[d] either: • Any clinical seizure, focal or generalized, that resolves rapidly, or • Non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, Or raised intracranial pressure: focal/local edema on neuroimaging.[d]	• Permanently discontinue epcoritamab. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. • Continue dexamethasone use until resolution to Grade 1 or less, then taper. • If no response, initiate methylprednisolone 1 000 mg/day • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care. • If an ICANS should occur, manage it according to the current practice guidelines.
Grade 4	ICE score 0[c], Or depressed level of consciousness[d]: either:	• Permanently discontinue epcoritamab.

Grade[a]	Presenting Symptoms[b]	Actions
	• Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • Stupor or coma Or seizures,[d] either: • Life-threatening prolonged seizure (> 5 minutes), or • Repetitive clinical or electrical seizures without return to baseline in between, Or motor findings[d]: • Deep focal motor weakness, such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema,[d] with signs/symptoms such as: • Diffuse cerebral edema on neuroimaging, or • Decerebrate or decorticate posturing, or • Cranial nerve VI palsy, or • Papilledema, or • Cushing's triad.	• Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care. • If an ICANS should occur, manage it according to the current practice guidelines.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.

[b] Management is determined by the most severe event, 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 (names 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

Grade[a]	Presenting Symptoms[b]	Actions
(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] Not attributable to any other cause. [e] Refer to section "Delayed administration" for information on restarting epcoritamab after dosage delays (see "Dosage/Administration"). [f] All references to dexamethasone administration are dexamethasone or equivalent.		

Table 6: Recommended Dosage Modifications for Other Adverse Reactions

Adverse Reaction[1]	Severity[1]	Action
Infections (see "Warnings and Precautions")	Grades 1-4	• Withhold epcoritamab in patients with active infection, until the infection resolves.[2] • For Grade 4, consider permanent discontinuation of epcoritamab.
Neutropenia (see "Warnings and Precautions")	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.[2]
Thrombocytopenia (see "Warnings and Precautions")	Platelet count less than 50 x 10^9/L	• Withhold epcoritamab until platelet count is 50 x 10^9/L or higher.[2]
Other Adverse Reactions (see "Adverse Reactions")	Grade 3 or higher	• Withhold epcoritamab until the toxicity resolves to Grade 1 or baseline.[2]
[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.		

Adverse Reaction[1]	Severity[1]	Action
[2] For recommendations on restarting epcoritamab after dosage delays see “Delayed administration”.		

Delayed administration

Diffuse large B-cell lymphoma

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).

Follicular lymphoma

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 8 days between the intermediate dose (0.8 mg) and the second intermediate dose (3 mg), or
- If there are more than 14 days between the second intermediate dose (3 mg) and first full dose (48 mg), or
- If there are more than 6 weeks between any two 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 dosage instructions

Patients with renal disorders

Dose adjustments are not considered necessary in patients with mild to moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment to end-stage renal disease.

Patients with hepatic disorders

Dose adjustments are not considered necessary in patients with mild hepatic impairment. No dose recommendations can be made for patients with moderate to severe hepatic impairment.

Children and adolescents

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

Elderly patients

In patients with DLBCL in EPCORE NHL-1, 44 (32%) were ≥65 to <75 years of age and 29 (21%) patients were ≥75 years of age. No clinically meaningful differences in safety or efficacy were observed between patients ≥65 years of age compared with younger adult patients.

Mode of administration

Tepkinly should be administered by subcutaneous injection, preferably in the lower part of the abdomen or the thigh. Change of injection site from left or right side or vice versa is recommended especially during the weekly administration (Cycles 1-3).
For instructions on dilution of the medicinal product before administration, see “Instructions for dilution and administration”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Cytokine release syndrome (CRS)

Cytokine release syndrome, 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 greater 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 “Dosage/Administration”). Monitor patients for potential CRS following epcoritamab administration during Cycle 1 and in subsequent cycles as needed at the physician’s discretion. At the first signs or symptoms of CRS manage according to applicable practice guidelines. Counsel patients on the signs and symptoms associated with CRS and instruct patients 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 “Dosage/Administration”).
Patients should be monitored within proximity of a healthcare facility (or alternatively in an inpatient setting) for signs and symptoms of CRS and/or ICANS for 24 hours during Cycle 1 Day 1 and Day 8 (DLBCL) or during Cycle 1 Day 1, Day 8, Day 15 and Day 22 (FL).

Patients with DLBCL should be hospitalized 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.
Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, have been reported in patients receiving epcoritamab. HLH should be considered when the presentation of CRS is atypical or unresponsive and/or clinical manifestations of HLH such as prolonged fever, cytopenias, hyperferritinemia, coagulopathy and elevated liver enzymes are present. If HLH is suspected, withhold epcoritamab and initiate treatment for HLH per current practice guidelines.

Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS)

Epcoritamab can cause serious or life-threatening neurologic side effects, including immune effector cell-associated neurotoxicity syndrome (ICANS). 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.
The onset of ICANS can be concurrent with CRS, following resolution of CRS or in the absence of CRS.
Monitor patients for signs and symptoms of ICANS following epcoritamab administration during Cycle 1 and in subsequent cycles as needed at the physician's discretion. At the first signs or symptoms of ICANS manage according to applicable practice guidelines. Counsel patients on the signs and symptoms of ICANS and that the onset of events may be delayed. Instruct patients to contact their healthcare professional and seek immediate medical attention should signs or symptoms occur at any time. Delay or discontinue epcoritamab as recommended (see "Dosage/Administration").
Patients should be monitored within proximity of a healthcare facility (or alternatively in an inpatient setting) for signs and symptoms of CRS and/or ICANS for 24 hours during Cycle 1 Day 1 and Day 8 (DLBCL) or during Cycle 1 Day 1, Day 8, Day 15 and Day 22 (FL).
Patients with DLBCL should be hospitalized 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.

Serious infections

Treatment with epcoritamab may lead to an increased risk of infections. Serious infections, including fatal infections, were observed in patients treated with epcoritamab in clinical trials (see "Adverse Events").
Avoid administration of epcoritamab in patients with clinically significant active systemic infections. As appropriate, administer prophylactic antimicrobials (see "Dosage/Administration"). Prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) and herpes virus infections is strongly recommended, especially when steroids are used concomitantly (see "Dosage/Administration").
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.
Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported in patients treated with epcoritamab who have also received prior treatment with other immunosuppressive medications. If neurological symptoms suggestive of PML occur during epcoritamab therapy, treatment with epcoritamab should be discontinued and appropriate diagnostic measures initiated.

Tumor lysis syndrome (TLS)

TLS has been reported in patients receiving epcoritamab (see section “Undesirable effects”). 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.

Tumor flare

Tumour flare has been reported in patients treated with epcoritamab (see “Undesirable effects”). 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 and patients with CD20-negative FL treated with epcoritamab and it is possible that patients with CD20-negative DLBCL and patients with CD20-negative FL may have less benefit compared to patients with CD20-positive DLBCL and patients with CD20-positive FL, respectively. The potential risks and benefits associated with treatment of patients with CD20-negative DLBCL and FL with epcoritamab should be considered.

Hepatotoxicity

Elevated liver enzymes have been reported in patients treated with epcoritamab (see “Undesirable effects”), and a Grade 5 event occurred. Monitor liver enzymes and bilirubin at initiation and during treatment, if clinically indicated. Use local protocols/guidelines as appropriate for treatment.

Reactivation of hepatitis B

Reactivation may occur in patients treated with drugs directed against B cells of hepatitis B virus (HBV), which can lead to fulminant hepatitis and liver failure, sometimes even death. Patients with positive HBV serology should be monitored for clinical symptoms indicating HBV reactivation and laboratory tests should be carried out during treatment with epcoritamab.

Cytopenias

Epcoritamab can cause serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia (see “Undesirable effects”).
Monitor complete blood counts throughout treatment. Based on the severity of cytopenias, temporarily withhold or permanently discontinue epcoritamab (see “Dosage/Administration”).

Immunisation

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

Previous CAR-T therapy

A total of 12 out of 215 patients with relapsed/refractory follicular lymphoma and epcoritamab therapy had prior CAR-T therapy. These data are too limited to make a reliable statement about the effectiveness of epcoritamab in patients with relapsed/refractory follicular lymphoma who had prior CAR-T therapy. These patients had higher disease burden and more prior treatments compared to patients without prior CAR-T therapy. Patients with prior CAR-T therapy experienced higher frequency of adverse events compared to patients without prior CAR-T therapy.

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 21.84 mg of sorbitol per vial. Patients with hereditary fructose intolerance (HFI) should not receive this medicine unless absolutely necessary.

Interactions

No interaction studies have been performed.

CYP substrates

For certain CYP substrates, minimal changes in the concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with epcoritamab.
Epcoritamab causes release of cytokines that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur

after the first dose of epcoritamab on Cycle 1 Day 1 and up to 14 days after the first 48 mg dose on Cycle 1 Day 15, and during and after CRS (see “Warnings and Precautions”).

Pregnancy, lactation

Women of childbearing potential

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.

Pregnancy

There are no data on the use of epcoritamab in pregnant women. Animal reproduction studies have not been conducted with epcoritamab 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. 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.
Verify pregnancy status in females of reproductive potential prior to initiating epcoritamab treatment.

Lactation

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 least 4 months after the last dose.

Fertility

The effect of epcoritamab on male and female fertility is unknown. Animal studies with epcoritamab showed no effect on reproductive organs that would indicate impaired fertility. No fertility studies have been conducted with epcoritamab (see “Preclinical data”).

Effects on ability to drive and use machines

No formal studies on the effect of epcoritamab on the ability to drive and operate machines have been performed. 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.

Undesirable effects

Summary of the safety profile

The safety of epcoritamab was evaluated in a non-randomised, single-arm GCT3013-01 study in 382 patients with relapsed or refractory large B-cell lymphoma (N=167), follicular lymphoma (N=129) and follicular lymphoma (3-step step-up dose schedule N=86) 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 4.9 months (range: <1 to 30 months).
The most common adverse reactions (≥ 20%) were CRS, injection site reactions, fatigue, viral infection, neutropenia, musculoskeletal pain, pyrexia and diarrhoea.
Serious adverse reactions occurred in 50% of patients. The most frequent serious adverse reaction (≥10%) was cytokine release syndrome (34%). Forteen patients (3.7%) experienced a fatal adverse reaction (pneumonia in 9 (2.4%) patients, viral infection in 4 (1.0%) patients, and ICANS in 1 (0.3%) patient).
Adverse reactions that led to discontinuation occurred in 6.8% of patients. Discontinuation of epcoritamab due to pneumonia occurred in 14 patients (3.7%), viral infection in 8 (2.1%) patients, fatigue in 2 (0.5%) patients, and CRS, ICANS or diarrhoea occurred in 1 (0.3%) patient each.
Dose delays due to adverse reactions occurred in 42% of patients. Adverse reactions leading to dose delays (≥ 3%) were viral infections (17%), CRS (11%), neutropenia (5.2%), pneumonia (4.7%), upper respiratory tract infection (4.2%) and pyrexia (3.7%).

List of adverse reactions

Adverse reactions 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).

Table 7: Adverse reactions reported in patients with relapsed or refractory LBCL or FL treated with epcoritamab in GCT3013-01 study

System organ class / preferred term or adverse reaction	**All grades**
Infections and infestations	
Viral infection[a]	Very common (27.7%)
Cough	Very common (14.7%)
Pneumonia[b]	Very common (12.0%)
Upper respiratory tract infection[c]	Very common (11.5%)
Fungal infection[d]	Common
Sepsis[e]	Common
Cellulitis	Common

Neoplasm benign, malignant and unspecified (including cysts and polyps)	
Tumour flare	Common
Blood and lymphatic system disorders	
Neutropenia[f]	Very common (27.5%)
Anaemia[g]	Very common (16.5%)
Thrombocytopenia[h]	Very common (12.8%)
Lymphopenia[i]	Very common (10.2%)
Febrile neutropenia	Common
Immune system disorders	
Cytokine release syndrome[j]	Very common (55.8%)
Metabolism and nutrition disorders	
Decreased appetite	Very common (10.5%)
Hypokalaemia	Common
Hypophosphatemia	Common
Hypomagnesaemia	Common
Tumour lysis syndrome[k]	Common
Blood sodium decreased[t]	Common
Nervous system disorders	
Headache	Very common (15.4%)
Immune effector cell-associated neurotoxicity syndrome[j]	Common
Cardiac disorders	
Cardiac arrhythmias[l]	Common
Respiratory, thoracic and mediastinal disorders	
Pleural effusion	Common
Gastrointestinal disorders	
Diarrhoea	Very common (20.7%)
Abdominal pain[m]	Very common (18.6%)
Nausea	Very common (18.1%)
Vomiting	Common
Hepatobiliary disorders	
Alanine aminotransferase increased	Common
Aspartate aminotransferase increased	Common

Alkaline phosphatase increased	Common
Skin and subcutaneous tissue disorders	
Rash[n]	Very common (13.1%)
Pruritus	Common
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain[o]	Very common (26.7%)
Blood creatinine increased	Common
General disorders and administration site conditions	
Injection site reactions[p]	Very common (39.5%)
Fatigue[q]	Very common (32.2%)
Pyrexia[r]	Very common (21.7%)
Oedema[s]	Very common (16.2%)

Undesirable reactions from the post-marketing phase: haemophagocytic lymphohistiocytosis (see "Warnings and Precautions").

Adverse reactions were graded using NCI CTCAE version 5.0

[a]Viral infection includes COVID-19, cytomegalovirus chorioretinitis, cytomegalovirus colitis, cytomegalovirus infection, cytomegalovirus infection reactivation, gastroenteritis viral, herpes simplex, herpes simplex reactivation, herpes virus infection, herpes zoster, oral herpes, post-acute COVID-19 syndrome, and varicella zoster virus infection

[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, oral candidiasis and oropharyngeal 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] Events graded using American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria

[k] Clinical 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 macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and rash vesicular

[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]Injection site reactions include injection site bruising, injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site nodule, injection site oedema, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, and injection site urticaria.

[q]Fatigue includes asthenia, fatigue, and lethargy

[r]Pyrexia includes body temperature increased and pyrexia

[s]Oedema includes face oedema, generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling, and swelling face

[t]Blood sodium decreased includes blood sodium decreased and hyponatraemia

Description of specific adverse reactions and additional information

Cytokine release syndrome

2-step step-up dose schedule (large B-cell lymphoma and follicular lymphoma)

In study GCT3013-01, CRS of any grade occurred in 58% (171/296) of patients with large B-cell lymphoma and follicular lymphoma treated with epcoritamab at the 2-step step-up dose schedule. The incidence of Grade 1 was 35%, Grade 2 was 21%, and Grade 3 occurred in 2.4%. Recurrent CRS occurred in 21% of patients. CRS of any grade occurred in 9.8% of patients after the priming dose (Cycle 1 Day 1); 13% after the intermediate dose (Cycle 1, Day 8); 51% after the first full dose (Cycle 1, Day 15), 6.5% after the second full dose (Cycle 1 Day 22) and 3.7% 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 12 days). The median time to onset after the first full dose was 19.3 hours (range: <0.1 to 7 days). CRS resolved in 99% of patients, and the median duration of CRS events was 2 days (range 1 to 54 days).

Of the 171 patients that experienced CRS, the most common signs and symptoms of CRS included pyrexia 99%, hypotension 32% and hypoxia 16%. Other signs and symptoms of CRS in ≥3% of patients included chills (11%), tachycardia (including sinus tachycardia (11%)), headache (8.2%), nausea (4.7%), and vomiting (4.1%). Transient elevated liver enzymes (ALT or AST > 3xULN) were

concurrent with CRS in 4.1% of patients with CRS. See ”Dosing/Administration” and “Warnings and Precautions” for monitoring and management guidance.

3-step step-up dose schedule follicular lymphoma

In study GCT3013-01, CRS of any grade occurred in 49% (42/86) of patients treated with epcoritamab at the recommended follicular lymphoma 3-step step-up dose schedule. The incidence of Grade 1 was 40%, Grade 2 was 9%. There were no Grade ≥3 CRS events reported. Recurrent CRS occurred in 23% of patients. Most CRS events occurred during Cycle 1, where 48% of patients experienced an event. In Cycle 1, CRS occurred in 12% of patients after the priming dose (Cycle 1 Day 1), 5.9% of patients after the intermediate dose (Cycle 1 Day 8), 15% of patients after the second intermediate dose (Cycle 1 Day 15), and 37% of patients after the first full dose (Cycle 1 Day 22). The median time to onset of CRS from the most recent administered epcoritamab dose was 59 hours (range: 1 to 8 days). The median time to onset after the first full dose was 61 hours (range: 1 to 8 days). CRS resolved in 100% of patients and the median duration of CRS events was 2 days (range 1 to 14 days).

Serious adverse reactions due to CRS occurred in 28% of patients who received epcoritamab.

Dose delays due to CRS occurred in 19% of patients who received epcoritamab.

Of the 42 patients that experienced CRS at the recommended dose, the most common (≥10%) signs and symptoms of CRS included pyrexia (100%) and hypotension (14%). In addition to corticosteroid use, tocilizumab was used to manage CRS event in 12% of patients.

Immune effector cell-associated neurotoxicity syndrome

In study GCT3013-01, ICANS occurred in 4.7% (18/382) of patients treated with epcoritamab; 3.1% experienced Grade 1 and 1.3% experienced Grade 2. One patient (0.3%) experienced an ICANS event of Grade 5 (fatal). The median time to first ICANS onset from the start of epcoritamab treatment was 18 days (range: 8 to 141 days). ICANS resolved in 94% (17/18) of patients with supportive care. The median time to resolution of ICANS was 2 days (range: 1 to 9 days). In the 18 patients with ICANS, the onset of ICANS was prior to CRS in 11% of patients, concurrent with CRS in 44%, following onset of CRS in 17%, and in the absence of CRS in 28%.

Serious infections

Large B-cell lymphoma

In study GCT3013-01, serious infections of any grade occurred in 25% (41/167) of patients with large B-cell lymphoma treated with epcoritamab. The most frequent serious infections were 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.

Follicular lymphoma

In study GCT3013-01, serious infections of any grade occurred in 32% (68/215) of patients with follicular lymphoma treated with epcoritamab. The most frequent serious infections included COVID-19 (8.8%), COVID-19 pneumonia (5.6%), pneumonia (3.7%), urinary tract infection (1.9%), and pneumocystis jirovecii pneumonia (1.4%). The median time to onset of first serious infection from the start of epcoritamab treatment (Cycle 1 Day 1) was 81 days (range: 1 to 636 days), with median duration of 18 days (range: 4 to 249 days). Grade 5 events of infection occurred in 8 (3.7%) patients, 6 (2.8%) of which were attributed to COVID-19 or COVID-19 pneumonia.

Tumor lysis syndrome

In study GCT3013-01, TLS occurred in 1.0% (4/382) of patients. Median time to onset was 18 days (range 8 to 33 days), and median duration was 3 days (range 2 to 4 days).

Cytopenia

Thrombocytopenia, anemia and lymphopenia occurred in 12.8% (49/382), 16.5% (63/382), and 10.2% (39/382) of patients, including 5.5%, 7.1%, and 8.9% Grade 3-4 events, respectively.

In study GCT3013-01, neutropenia of any grade occurred in 28% (105/382) of patients, including 23% Grade 3-4 events. The median time to onset of first neutropenia/neutrophil count decreased event was 65 days (range: 2 to 750 days), with median duration of 15 days (range: 2 to 415 days). Of the 105 patients who had neutropenia/neutrophil count decreased events, 61% received G-CSF to treat the events.

CLIPPERS

One Grade 3 event of CLIPPERS occurred in 1 patient who was reported to have had CLIPPERS 106 days prior to the start of epcoritamab treatment.

Progressive multifocal leukoencephalopathy (PML)

PML occurred in two patients, of which 1 event of PML was fatal.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. The incidence of treatment-emergent ADAs with the 2-step step-up dose schedule (0.16/0.8/48 mg) in the combined population of DLBCL and FL was 3.4% (3.4 % positive, 93.9% negative and 2.7% indeterminate, N=261 evaluable patients) and 3.3% (3.3% positive, 95% negative and 1.7% indeterminate, N= 60 evaluable patients), in studies GCT3013-01 and GCT3013-04, respectively.

The incidence of treatment-emergent ADAs with the 3-step step-up dose schedule (0.16/0.8/3/48 mg) in the FL optimisation cohort was 7% (7% positive, 91.5% negative and 1.4% indeterminate, N=71 evaluable patients) in study GCT3013-01. A subject is classified as indeterminate if the patient is confirmed ADA positive at baseline but there is no confirmed positive on-treatment record or if confirmed ADA positive on treatment record titre are equal or lower than baseline.
No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited. Neutralising antibodies were not evaluated.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

L01FX27

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. CD20 is expressed on most human B-cell lymphomas and leukaemias and on B cells in peripheral blood, but not hematopoietic stem cells or plasma 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 as epcoritamab does not have direct immune effector mechanisms.

Pharmacodynamics

Epcoritamab induced rapid and sustained depletion of circulating B-cells (defined as CD19 B-cell counts ≤ 10 cell/µl) in subjects who have detectable B cells at treatment initiation. There were 21% subjects (n=33) with DLBCL and 50% subjects (n=56) with FL 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.
In study GCT3013-01, following subcutaneous administration of epcoritamab at the recommended 2-step step-up dose schedule in patients with LBCL, 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. Levels returned to baseline prior to the subsequent full dose , however elevations of cytokines could also be observed after Cycle 1.
In study GCT3013-01, following subcutaneous administration of epcoritamab at the recommended 3-step step-up dose schedule in patients with FL, median IL-6 levels associated with CRS risk remained consistently low after each dose in Cycle 1 and beyond, particularly after the first full dose, compared to patients who received the 2-step step-up dose.

Clinical efficacy

Diffuse large B-cell lymphoma

Study EPCORE NHL-1 was an open-label, multi-cohort, multicentre, single-arm trial 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 excluded patients with CNS involvement of lymphoma**,** 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 and cardiac ejection fraction less than less than 45%. Efficacy was evaluated in 139 patients with DLBCL who had received the 48 mg full dose SC in cycles of 4 weeks, i.e., 28 days. Epcoritamab monotherapy was administered at the recommended 2-step step-up dose schedule 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 8.

Table 8: Demographics and baseline characteristics of patients with DLBCL in EPCORE NHL-1 study

Characteristics	**(N=139)**
Age	
Median, years (min, max)	66 (22, 83)
Males (%)	61
Race	
White (%)	60
Asian (%)	19
Other	4
Not Reported	17

ECOG performance status (%)	
0	48
1	48
2	4
Number of prior lines of anti-lymphoma therapy (%)	
Median (min, max)	3 (2, 11)
2	30
3	34
≥4	37
DLBCL Disease history (%)	
De Novo DLBCL	70
DLBCL transformed from indolent lymphoma	29
FISH Analysis Per Central lab, N=88	
Double-hit/Triple-hit lymphoma (%)	14
Prior therapy (%)	
Prior CAR-T	38
Prior autologous HSCT	19
Primary refractory disease[a]	59
Refractory to ≥2 consecutive lines of prior anti-lymphoma therapy[b]	75
Refractory to the last line of systemic antineoplastic therapy[b]	82
Refractory to prior anti-CD20 therapy	84
Refractory to CAR-T	28
[a]A patient is considered to be primary refractory if they are refractory to frontline anti-lymphoma therapy. [b]A patient is considered to be refractory if they experience disease progression or stable disease as best response or disease progression within 6 months after therapy completion. Data cut: 31 Jan 2022	

Efficacy was established based on overall response rate (ORR) determined by Lugano criteria (2014) as assessed by Independent Review Committee (IRC). The median follow-up time was 15.5 months (range: 0.3 to 21 months) in patients with DLBCL who had prior CAR-T or who were not eligible for CAR-T.

Table 9: Efficacy results in study EPCORE NHL-1 in patients with DLBCL who had prior CAR-T or who were not eligible for CAR-T

Endpoint **IRC assessment**	**Epcoritamab** **(N=87)**
ORR[a], n (%)	49 (56)
(95% CI)	(45.3, 66.9)
CR, n (%)	27 (31)
(95% CI)	(21.5, 41.9)
PR, n (%)	22 (25)
DOR	
Median (95% CI), months	15.6 (4.0, NR)
DOR if Best Response is CR	
Median (95% CI), months	15.6 (15.6, NR)
CI = confidence interval; CR = complete response; DOR = duration of response; IRC = independent review committee; NR = not reached; ORR = overall response rate [a] Determined by Lugano criteria (2014) as assessed by independent review committee (IRC)	

The median time to CR was 2.8 months (range: 1.2 to 10.2 months).
Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 9).
Median overall survival (OS) for patient on epcoritamab was 14.7 (8.2, not reached).

Follicular lymphoma
Study GCT3013-01 was an open-label, multi-cohort, multicentre, single-arm trial that evaluated epcoritamab as monotherapy in patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. The study includes a dose escalation part, an expansion part and a 3-step step-up dose optimisation 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 iNHL cohort, included patients with FL. 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 with histologic confirmed FL 1-3A at initial diagnosis without clinical or pathological evidence of transformation. All patients had relapsed or refractory disease to the last prior line therapy and previously treated with at least 2 lines of systemic antineoplastic therapy, including at least 1 anti-CD20 monoclonal antibody-containing therapy and an alkylating agent or lenalidomide. The study excluded patients with CNS involvement

of lymphoma, allogeneic HSCT or solid organ transplant, ongoing active 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 and cardiac ejection fraction less than 45%. Efficacy in the expansion cohort was evaluated in 128 patients who had received epcoritamab subcutaneously (SC) in cycles of 4 weeks, i.e., 28 days. Epcoritamab was administered as a monotherapy in a 2-step step-up dose schedule as follows:

- Cycle 1: epcoritamab 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Day 15 and 48 mg on 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 median number of cycles initiated was 8 and 60% received 6 cycles.

Among the 128 patients with FL, the median age was 65 years (range: 39 to 84), 48% (61/128) were less than 65 years of age, 39% (50/128) were between 65 to less than 75 years of age, 13% (17/128) were 75 years of age or older. Sixtytwo percent (79/128) were male. Sixty percent were White, 6% were Asian, 1.6% others and 33% did not report race. A total of 85% had stage III-IV disease, 26% had bulky disease, 24% had a FLIPI score of 2, 61% had a FLIPI score of 3-5; 55% had an ECOG performance status of 0, 40% had an ECOG performance status of 1, and 6% had an ECOG performance status of 2. The median number of prior therapies was 3 (range: 2 to 9), with 37% receiving 2 prior lines of systemic therapy, 32% receiving 3 prior therapies, and 31% receiving 4 or more prior therapies.
Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy, 70% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 55% refractory to ≥2 consecutive lines of prior anti-lymphoma therapy, 69% were refractory to the last line of systemic antineoplastic therapy, 21% had prior rituximab plus lenalidomide therapy, 19% received prior autologous HSCT, 5% received prior chimeric antigen receptor (CAR) T-cell therapy, 23% PI3K inhibitor. Fifty-two percent of patients had progression of disease within 24 months of first systemic therapy.

Efficacy was established based on overall response rate (ORR) determined by Lugano criteria (2014) as assessed by Independent Review Committee (IRC). The median follow-up for DOR was 16.2 months. Efficacy results are summarised in Table 10.

Table 10: Efficacy Results in Study GCT3013-01 in FL Patients

Endpoint [a] **IRC assessment**	**Epcoritamab** **(N=128)**
ORR [b], n (%)	106 (83)
(95% CI)	(75.1, 88.9)
CR[b], n (%)	81 (63)
(95% CI)	(54.3, 71.6)
PR [b], n (%)	25 (20)
(95% CI)	(13.1, 27.5)
DOR[b]	
Median (95% CI), months	21.4 (13.7, NR)
DOCR[b]	
Median (95% CI), months	NR (21.4, NR)
12-month estimate, % (95% CI)	78.6 (67.3, 86.4)
TTR, median (range), months	1.4 (1, 3)
CI = confidence interval; CR = complete response; DOR = duration of response; DOCR = duration of complete response; IRC = independent review committee; ORR = overall response rate; PFS = progression-free survival; 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. Data cut: 16 October 2023	

The median time to CR was 1.5 months (range: 1.2 to 11.1 months).

Pharmacokinetics

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.

Epcoritamab maximum concentration (10.2 mcg/mL [43.2%]) is achieved after the first dose of the Q2W regimen (i.e., the first dose of Cycle 4). No clinically significant differences in pharmacokinetic parameters were observed between patients with relapsed or refractory LBCL and patients with relapsed or refractory FL. PK exposures are summarized for the recommended dosage of epcoritamab in Table 11.

Table 11: Exposure Parameters of Epcoritamab in Subjects with Relapsed or Refractory LBCL and Relapsed or Refractory FL Following Recommended Dosage

	C_{avg} (mcg/ml)[1]	C_{max} (mcg/ml)[1]	C_{trough} (mcg/ml)[1]
First full 48 mg dose[2]	1.3 (113.3%)	1.7 (106.7%)	1.4 (100.9%)
End of weekly dosing (end of Cycle 3)	9.1 (45.9%)	9.9 (43.4%)	7.8 (52.4%)
End of every 2-week dosing (end of Cycle 9)	5.3 (57%)	6.7 (49.4%)	3.6 (81.5%)
Steady state[3] with every 4-week dosing	2.4 (73.3%)	4.2 (59.8%)	1.1 (134.1%)
[1] Values are geometric mean with geometric CV% [2] First full 48 mg dose is on the first day of Week 3 in subjects with relapsed or refractory LBCL and on the first day of Week 4 in subjects with relapsed or refractory FL [3] Steady state values are approximated at Cycle 15 (Week 60)			

Epcoritamab exposures are similar between FL subjects who received the 3-step step-up dose schedule and 2-step step-up dose schedule except for transiently lower trough concentrations, as expected, at Cycle 1 Day 15 after the second intermediate dose (3 mg) with 3-step step-up dose schedule compared to first full 48 mg dose with 2-step step-up dose schedule.

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 the apparent volume of distribution at steady state is 25.61 L (81.8%) based on population PK modelling.

Metabolism

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.

Kinetics in specific patient groups

No clinically important effects on the pharmacokinetics of epcoritamab were observed based on age (20 to 89 years), sex, or race/ethnicity (white, Asian, and other), mild to moderate renal impairment (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 172 kg) has a statistically significant effect on the pharmacokinetics of epcoritamab, however this effect is not clinically relevant across body weight categories (<65kg, 65-<85, ≥85).

Children and adolescents

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

Preclinical data

Repeated dose toxicity

Effects in the repeat-dose toxicity studies in cynomolgus monkeys were generally consistent with the pharmacologic mechanism of action of epcoritamab. 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/Carcinogenicity

Genotoxicity and carcinogenicity of epcoritamab were not examined.

Reproductive toxicity

Animal fertility studies have not been conducted with epcoritamab, however, in an intravenous general toxicity study of 5 weeks duration, epcoritamab caused no toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses up to 1 mg/kg/week. 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.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Chemical and physical in-use stability has been demonstrated for 24 hours at 30 °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. Within these 24 hours, the epcoritamab solution can be stored at room temperature for 12 hours from the time of preparation to administration.
Minimise exposure to daylight.
Allow epcoritamab solution to equilibrate to room temperature before administration.
Discard unused epcoritamab solution beyond the allowable storage time.

Special precautions for storage

Store in the refrigerator (2–8 °C).
Do not freeze.
Do not shake.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

Preparation of epcoritamab

This entire section must be read carefully before preparation of epcoritamab. **Certain doses** (the priming (0.16 mg) and intermediate dose (0.8 mg)) of epcoritamab require **dilution** prior to administration. Epcoritamab can be diluted using two different methods which are either the vial method or the syringe method.
All instructions provided below must be followed as improper preparation may lead to improper dose.
Epcoritamab must be prepared and administered by a healthcare provider as a subcutaneous injection. Each vial of epcoritamab is intended for single dose only.
The administration of epcoritamab takes place over the course of 28-day cycles, following the dosing schedule in “Dosage/Administration”.
Parenteral drug products should be inspected visually for particulate matter and discoloration

prior to administration, whenever solution and container permit.

Use aseptic technique to prepare the priming and intermediate dose of epcoritamab. Filtration of the diluted solution is not required.

Preparation instructions for 0.16 mg and 0.8 mg doses of epcoritamab using the empty sterile vial method

0.16 mg priming dose preparation instructions **– 2 dilutions required** – empty sterile vial method

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

1)	Prepare epcoritamab vial a) Retrieve one vial of epcoritamab 4 mg/0.8 ml vial 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** invert, 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 vial labelled as **dilution A**. c) Transfer **4.2 ml of 0.9% sodium chloride injection**, sterile solution, into the vial labelled as **dilution A**. 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 **2.0 ml of solution** from the vial labelled as **dilution A** into the vial labelled as **dilution B**. The **dilution A** vial is no longer needed and should be discarded. c) Transfer **8.0 ml of 0.9% sodium chloride injection**, sterile solution, into the vial labelled as **dilution B** 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 **1.0 ml of the diluted epcoritamab** from the **dilution B** vial into a syringe.
5)	Label syringe Label the syringe with the medicinal product name, dose strength (0.16 mg), date and the time of day.
6)	Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

0.8 mg intermediate dose preparation instructions **– 1 dilution required** – empty sterile vial method

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 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** invert, 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 vial labelled as **dilution A**. c) Transfer **4.2 ml of 0.9% sodium chloride injection**, sterile solution, into the vial labelled as **dilution A** 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 **1.0 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 medicinal product name, dose strength (0.8 mg), date and the time of day.
5)	Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

Preparation instructions for 0.16 mg and 0.8 mg doses of epcoritamab using the sterile syringe method

0.16 mg priming dose preparation instructions **– 2 dilutions required** – sterile syringe method

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

1)	Prepare epcoritamab vial a) Retrieve one 4 mg/0.8 ml epcoritamab vial 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** invert, vortex, or vigorously shake the vial.
2)	Perform first dilution a) Label an appropriately sized syringe as "**dilution A**". b) Withdraw **4.2 ml of 0.9% sodium chloride injection, sterile solution,** into the syringe labelled as **dilution A**. Include approximately 0.2 ml air in the syringe. c) In a new syringe labelled as "**syringe 1**", withdraw **0.8 ml of epcoritamab**. d) Connect the two syringes and push the **0.8 ml of epcoritamab** into the syringe labelled as **dilution A**. The initially diluted solution contains 0.8 mg/ml of epcoritamab. e) Gently mix by inverting the connected syringes 180 degrees 5 times.

	f) Disconnect the syringes and discard **syringe 1**.
3)	Perform second dilution a) Label an appropriately sized syringe as "**dilution B**". b) Withdraw **8 ml of 0.9% sodium chloride injection, sterile solution,** into the syringe labelled as **dilution B**. Include approximately 0.2 ml air in the syringe. c) Label another appropriately sized syringe as "**syringe 2**". d) Connect **syringe 2** to the **dilution A** syringe and transfer **2 ml of solution** into **syringe 2**. The **dilution A** syringe is no longer needed and should be discarded. e) Connect **syringe 2** to the **dilution B** syringe and push the **2 ml of solution** into the syringe labelled as **dilution B** to make a final concentration of 0.16 mg/ml. f) Gently mix by inverting the connected syringes 180 degrees 5 times. g) Disconnect the syringes and discard **syringe 2**.
4)	Withdraw dose Connect and transfer **1 ml of the diluted epcoritamab** from the **dilution B** syringe into a new syringe. The **dilution B** syringe is no longer needed.
5)	Label syringe Label the syringe with the medicinal product name, dose strength (0.16 mg), date and the time of day.
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** – sterile syringe method</u>

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

1)	Prepare epcoritamab vial a) Retrieve one epcoritamab 4 mg/0.8 ml vial 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** invert, vortex, or vigorously shake the vial.
2)	Perform dilution a) Label an appropriately sized syringe as "**dilution A**". b) Withdraw **4.2 ml of 0.9% sodium chloride injection, sterile solution,** into the **dilution A** syringe. Include approximately 0.2 ml air in the syringe. c) In a new syringe labelled as "**syringe 1**", withdraw **0.8 ml of epcoritamab**. d) Connect the two syringes and push the **0.8 ml of epcoritamab** into the **dilution A** syringe to make a final concentration of 0.8 mg/ml.

	e) Gently mix by inverting the connected syringes 180 degrees 5 times. f) Disconnect the syringes and discard **syringe 1**.
3)	Withdraw dose Connect a new syringe to the **dilution A** syringe and transfer **1 ml of the diluted epcoritamab** into the new syringe. The **dilution A** syringe is no longer needed and should be discarded.
4)	Label syringe Label the syringe with the medicinal product name, dose strength (0.8 mg), date and the time of day.
5)	Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

Preparation of 3 mg epcoritamab dose

3 mg second intermediate dose preparation instructions **– No dilution required**

Epcoritamab 3 mg dose is required for FL patients only (see “Dosage/Administration”).

1)	Prepare epcoritamab vial a) Retrieve one epcoritamab 4 mg/0.8 ml vial 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** invert, vortex, or vigorously shake the vial.
2)	Withdraw dose Withdraw **0.6 ml of epcoritamab** into a syringe.
3)	Label syringe Label the syringe with the medicinal product name, dose strength (3 mg), date and the time of day.
4)	Discard the vial and any unused portion of epcoritamab in accordance with local requirements.

Site administration

The injection site should be preferably in the lower part of abdomen or the thigh. Change of injection site from left or right side or vice versa is recommended especially during the weekly administration (Cycles 1-3).

Authorisation number

69161 (Swissmedic)

Packs

Tepkinly 4 mg/0,8 ml, solution for injection: 1 vial [A]

Marketing authorisation holder

AbbVie AG, 6330 Cham

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