Taiwan Food and Drug Administration

Assessment Report

Trade Name：利癌妥注射劑/ Columvi solution for infusion

Active Ingredient：Glofitamab

License Number：MOHW-BI 001232

Applicant：羅氏大藥廠股份有限公司

Approval Date：112/07/27

Indication：
適用於治療先前曾接受至少兩線全身治療之復發性或難治性瀰漫性大 B 細胞淋巴瘤(DLBCL)的成人病人。
本適應症係依據腫瘤完全反應率(complete response rate)及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

Columvi 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.
This indication is approved under accelerated approval based on complete response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Background Information

Trade Name	利癌妥注射劑 Columvi solution for infusion
Active Ingredient(s)	Glofitamab
Applicant	羅氏大藥廠股份有限公司
Dosage Form & Strengths	注射液劑 1 毫克/毫升
Indication	適用於治療先前曾接受至少兩線全身治療之復發性或難治性瀰漫性大 B 細胞淋巴瘤(DLBCL)的成人病人。 本適應症係依據腫瘤完全反應率(complete response rate)及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 Columvi 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. This indication is approved under accelerated approval based on complete response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
Posology	詳見仿單
Pharmacological Category ATC Code	L01FX28

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

Glofitamab is a [2+1] bispecific humanized mAb and consists of two different heavy chains and two different light chains. Glofitamab contains two Fab domains directed against the human CD20 protein (in a bivalent binding mode) and one Fab domain directed against the human CD3ε subunit of the T-Cell receptor. Glofitamab is a human IgG1 with the Fc region bearing a proprietary modification, which abrogates its binding to Fc gamma receptors (FcγR), and prevents FcγR-mediated co-activation of innate immune effector cells including natural killer cells, monocytes/macrophages, and neutrophils without changes in functional binding to FcRn (neonatal Fc receptor).

A list of raw materials used in the drug substance (DS) manufacturing process has been provided. Raw materials are tested according to pharmacopoeia or according to in-house specifications. No animal- or human-derived materials are used during the manufacture of DS with the exception of the cell substrate.

Master cell bank (MCB) and Working cell banks (WCB) were manufactured under GMP conditions. The tests for detection of non-viral and viral adventitious agents have been conducted on MCB and WCB (LIVCA cells). All cell banks were found to be free from bacterial, fungal, and mycoplasma contamination as well as adventitious viruses. The cell substrate stability has been confirmed with respect to genetic consistency, consistent production of glofitamab, and retention of appropriate cell growth and cell viability after storage under defined storage conditions.

The manufacturing process of DS is described in sufficient detail. The process parameters and in-process testing are considered adequate. The DS manufacturing process has been satisfactorily validated and is capable of producing consistent and acceptable product quality for DS.

The DS has been characterized extensively on primary structure, higher-order structure, product-related substances, product-related impurities, and biological activity. Removal of other process-related impurities has been demonstrated during process validation.

The specifications of DS have been adequately justified and the proposed acceptance criteria are considered appropriate. The analytical procedures have been described and validated in line with ICH Q2(R1). The batch analysis results were consistent and within the defined acceptance criteria in place at the time of manufacture.

Several glofitamab DS batches have been placed on long-term, accelerated and stress stability studies. On the basis of the data provided, the approvable shelf life for DS is 42 months at recommended long-term storage conditions.

2.1.2 Drug Product

The glofitamab drug product (DP) is a sterile, colorless concentrate for solution for infusion with no preservatives. The DP is formulated as 1 mg/mL glofitamab and there are two DP configurations: 6 mL vial contains 2.5 mg (nominal) of glofitamab and 15 mL vial contains 10 mg (nominal) of glofitamab. All excipients used in the DP formulation are compliant with relevant compendial monographs. No novel excipients and no excipients of human or animal origin are used.

The DP manufacturing process consists of dilution/mixing, bioburden reduction filtration, sterile filtration, aseptic filling, stoppering, capping, and visual inspection. The process parameters and process controls are provided with justified acceptance limits/ranges. The DP manufacturing process has been fully validated to ensure consistent and acceptable product quality when run at commercial manufacturing site.

The release specifications and stability specifications for DP include appearance, general characteristic properties, quantity, identity, purity/impurity, potency by cell-based bioassay, endotoxins and sterility. The justifications for the specifications are accepted.

The DP is stored in a Type I glass vial with a rubber stopper sealed by an aluminum crimp seal. The suitability for the container closure system has been demonstrated.

The stability data from long-term conditions supports a proposed 24-month shelf life for DP when stored at the recommended storage conditions of 5 ± 3°C.

In conclusion, the information on the DS and DP is sufficiently detailed and the overall quality of glofitamab is considered acceptable.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro and *in vivo* studies have demonstrated that glofitamab mediated potent B-cell killing by engaging and activating T cells. It is broadly active against a wide range of CD20-expressing DLBCL tumor cell lines and primary NHL tumors, including the low CD20-expressing ones, thus providing promising therapeutic potential for the treatment of B-cell hematologic malignancies. Glofitamab maintained potent anti-tumor activity when administered with regimens applied to mitigate cytokine release, including a single administration of obinutuzumab prior to the first infusion of glofitamab, step-up dosing, and dexamethasone premedication.

Safety pharmacology investigations of the potential effects on major physiological systems (cardiovascular, respiratory, and central nervous system) were incorporated into the designs for toxicology studies. Treatment-related increases in heart rate and body temperature were observed, which was considered to be related to increases in cytokine levels following dosing. No test article-related findings on respiration, and no clinical signs specifically related to effects on CNS were observed.

2.2.2 Toxicological Studies

In the pivotal repeated-dose toxicity studies included a 4-week study in monkeys, findings were consistent with glofitamab-induced T-cell activation and cytokine release, as well as findings secondary to cytokine release like clinical signs, acute phase reactions, and changes in leukocyte trafficking (activation and redistribution). The absence of genotoxicity and carcinogenicity studies was agreed since glofitamab is an antibody not expected to interact with DNA or to be carcinogenic. Safety margins calculated for key toxicity studies are 0.28 fold for AUC and 0.36 for C_{max} relative to the selected 30 mg human dose.

Reproductive and developmental toxicity studies have not been conducted with glofitamab. The available nonclinical and clinical data for glofitamab and the known risks associated with other approved anti-CD20 antibody drugs indicate an overall risk to pregnancy (due to cytokine release and/or infections) but a low risk for teratogenicity.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Non-compartmental analyses indicated that glofitamab serum concentration reaches the maximal level (C_{max}) at the end of infusion and declines in a bi-exponential fashion. Glofitamab exhibits linear and dose-proportional pharmacokinetics in the dose range studied (0.005 to 30 mg) and is independent of time. Glofitamab is administered intravenously, with an absolute bioavailability of 1.0. The central volume of distribution (V_1) was 3.33 L and peripheral volume of distribution (V_2) was 2.18 L. Glofitamab is a human mAb that is degraded by proteolytic enzymes widely distributed in the body.

The serum concentration-time data was well-described by the population pharmacokinetic (PopPK) model with two compartments and both time-independent and time-varying clearance pathways. The time-independent clearance pathway was estimated as 0.602 L/day and the initial time-varying clearance pathway (CLT_0) as 0.396 L/day, with a relatively quick exponential decay over time (K_{des} ~ 0.445 day^{-1}). The estimated decay half-life from the initial total clearance value to the time-independent clearance only (HL_{trans}) was estimated as 1.56 days. The half-life in the linear phase (i.e., after the contribution of time-varying clearance collapsed to a negligible amount) can be approximated to be 6.54 days based on the Pop PK model.

2.3.2 Interaction Studies

Inhibitors or inducers of CYP, or of transporters such as P-glycoprotein, are not expected to affect the pharmacokinetics of glofitamab, as a victim of drug-drug interactions (DDIs).

Physiologically based pharmacokinetic (PBPK) modelling demonstrated the magnitude of the suppressive effect of transient IL-6 increase on hepatic CYP enzyme activities is only mild,

being lower than 50%. Moreover, the changes in exposures to sensitive substrates of CYP3A4, CYP1A2, and CYP2C9 are expected to show only a maximum twofold increase in exposure in the worst-case scenario.

Consideration may be given during the first cycle in patients who are receiving concomitant CYP substrates with a narrow therapeutic index. In these patients, monitoring for toxicity (e.g., warfarin) or for drug concentrations (e.g., cyclosporine) may be warranted.

2.3.3 Special Populations

Pop PK modeling based on Study NP30179 in patients indicated no clinically meaningful effect of body weight, age and gender on glofitamab pharmacokinetics.

The effect of renal impairment on glofitamab PK was investigated in the Pop PK model based on creatinine clearance (CrCL) values from Study NP30179. Among the 399 PK-evaluable patients, 195 patients (48.9%) had normal renal function at baseline, 141 patients (35.3%) had mild renal impairment, 62 patients (15.5%) had moderate renal impairment, and 1 patient (0.25%) had severe renal impairment. The results indicated that CrCL did not affect glofitamab PK. No dose adjustment of glofitamab is required in patients with mild or moderate renal impairment. However, the number of patients with severe renal impairment was limited (n=l) and no patients on dialysis have been studied, therefore a recommended dose for glofitamab has not been determined for these patients..

From the 399 PK-evaluable patients in Study NP30179, 347 had normal hepatic function, 48 had mild impaired function, 2 had moderate impaired function, 1 had severe hepatic impaired function and the information about hepatic function was unavailable for 1 patient. The pharmacokinetics of glofitamab in patients with mild hepatic impairment were similar to those with normal hepatic functions. No dose adjustment is required in patients with mild hepatic impairment. The PK of glofitamab has not been evaluated in a sufficient number of patients with moderate or severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study NP30179 is an ongoing Phase I/II, multicenter, open-label, dose expansion and dose escalation study of glofitamab in patients with R/R B-cell NHL. The application was supported with data from Part III expansion Cohort D3, including 108 patients with R/R DLBCL who received ≥ 2 prior systemic therapies and were treated at the proposed registrational dose of 2.5/10/30 mg after pre-treatment with a single dose of obinutuzumab. Patients were predominantly white (74.1%), male (69.4%) with a median age of 66.0 years (range: 21-90). The most common histological cancer subtype was DLBCL-NOS (71.3%), followed by trFL

(15.7%). 73.1% had Ann Arbor stage III/IV disease and 40.7% had bulky disease defined as tumor lesions measuring > 6 cm. Extranodal disease was reported in 64.8% of patients. These patients had received a median of 3 (range: 2-7) prior cancer therapies. The overall median duration of follow-up was 15 months (range: 0 to 21 months).

The IRC-assessed CR rate of 35.2% (95% CI: 26.2, 45.0) was statistically significantly higher than the historical control CR rate (20%) with a p-value < 0.0001. The IRC-assessed overall response rate was 50.0% (95% CI: 40.2, 59.8). The median duration of CR (DOCR) was not reached (95% CI: 18.4, NE) and the median duration of response (DOR) was 14.4 months (95% CI: 8.6, NE). The median of IRC-assessed PFS was 3.7 months (95% CI: 3.3, 6.8).

2.4.2 Safety Results

Almost all patients (98.7%) in the primary safety population (N=154) treated with obinutuzumab pretreatment or glofitamab 2.5/10/30 mg step-up dosing experienced at least one AE. Grade ≥ 3 AEs were reported in 98 patients (63.6%). SAEs were reported in 75 patients (48.7%); AEs in 140 patients (90.9%) were assessed as related to glofitamab by the investigator. The frequency of patient discontinuation due to AEs in the study was 9.1%.

The most frequent AEs reported in the primary safety population were cytokine release syndrome (CRS) (64.3% by ASTCT grading, Grade 3-4 3.9%), neutropenia/neutrophil count decreased (37.7%), anemia (30.5%), thrombocytopenia/platelet count decreased (24.7%) and neurologic adverse events (38.3%, Grade ≥ 3 2.6%). Other safety concerns included hepatotoxicity, infection and tumor flare.

CRS AEs were common despite use of obinutuzumab pre-treatment, and the occurrence of recurrent events was observed. 7 patients (7.1%) required ICU admission for CRS. Neurological AEs consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) were reported in 11 patients (7.1%), including one Grade 5 event.

2.5 Bridging Study Evaluation

The glofitamab Pop PK analysis dataset from study NP30179 included 320 (80.2%) White, 3 (0.752%) Black or African American, 16 (4.04%) Asian and 60 (15%) other/unknown race patients. Taiwan was the only Asian country recruiting patients in Study NP30179 (n=11) while a further 5 Asian patients were recruited in Australia. The individual estimates from the Pop PK model did not suggest any trend toward a difference in glofitamab PK parameters by race.

Within Study NP30179 (Cohort D3; 2.5/10/30 mg glofitamab), the Cmax of Asian patients (n=6) were similar to non-Asian patients (n=96). Similarly, the $AUC_{0\text{-last}}$ of Asian patients (n=6) at 2.5 mg was within the range of non-Asian patients (n=96). At 10 mg and 30 mg, the $AUC_{0\text{-}}$

$_{last}$ was slightly higher in Asian patients (n=5), than non-Asian (n=96) patients. In conclusion, there is no clinically meaningful difference in PK between Asian and non-Asian populations.

As Study Y042610 was a study conducted solely in China, the 12 R/R DLBCL patients included in the interim analysis were Asian by race and from the China region. The key PK parameters (from Non-compartmental analysis) for serum glofitamab were comparable between Asian patients from Study Y042610 (PK cohort; n=12; 2.5/10/30 mg glofitamab) and non-Asian patients from Study NP30179 (Cohort D3; n=96; 2.5/10/30 mg glofitamab). As such, no ethnic difference between Asian and non-Asian patients were observed for the key PK parameters (Cmax, AUC_{last}, CL, and Vz).

The PK of glofitamab was broadly linear (0.005 to 30 mg). It's not a steep exposure-response curve for efficacy and not a narrow therapeutic range. Glofitamab, a monoclonal antibody, is eliminated via catabolic degradation without the involvement of CYP450 isoforms, there is low potential for drug-drug interactions. In addition, as glofitamab is administered via IV infusion there is minimal potential for drug-diet interactions. Overall, no clinically meaningful difference in the pharmacokinetics of glofitamab was observed among Taiwanese, Asian (non-Taiwanese), and non-Asian patients. As such, no adjustment of dose nor a PK bridging study is warranted for Asian patients.

Based on the results of Taiwanese subgroup, the overall benefit-risk assessment of glofitamab IV monotherapy in Taiwanese subgroup with R/R DLBCL who have relapsed multiple times to several classes of prior anti-cancer treatment was not different from the overall population of patients of predominantly White race enrolled in the NP30179 study. However, these data should be interpreted with caution due to the limited number of Taiwanese patients.
Therefore, a conditional bridging study waiver was recommended.

Requirement for conditional waiver: Submit the final results and East Asian subgroup analysis of study STARGLO (GO41944).

2.6 Conclusion

This multidisciplinary review recommends accelerated approval for Columvi solution for infusion (glofitamab) for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
This indication is approved under accelerated approval based on complete response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

3. Post-Marketing Requirements

Submit the CSR including the East Asian subgroup analysis of the confirmatory study, Study GO41944 (A Phase III, Open-Label, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Glofitamab in Combination With Gemcitabine Plus Oxaliplatin Versus Rituximab in Combination With Gemcitabine and Oxaliplatin in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma) after trial completion.