Taiwan Food and Drug Administration

Assessment Report

Trade Name：保癌寧 凍晶注射劑 / POLIVY

Active Ingredient：Polatuzumab vedotin

License Number：MOHW-BI 001123

Applicant：羅氏大藥廠股份有限公司

Approval Date：2020/03/30

Indication：

POLIVY 與 bendamustine 和 rituximab 併用，適用於治療復發型 (relapsed) 或難治型 (refractory) 且不適合接受造血幹細胞移植的瀰漫性大型 B 細胞淋巴瘤 (DLBCL) 病人。

本適應症係依據完全反應率(complete response rate)獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

POLIVY in combination with bendamustine and rituximab is indicated for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for hematopoietic stem cell transplant.

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

1. Background Information

Trade Name	保癌寧 凍晶注射劑 / POLIVY
Active Ingredient(s)	Polatuzumab vedotin
Applicant	羅氏大藥廠股份有限公司
Dosage Form & Strengths	Lyophilized powder for injection
Indication	POLIVY 與 bendamustine 和 rituximab 併用，適用於治療復發型 (relapsed) 或難治型 (refractory) 且不適合接受造血幹細胞移植的瀰漫性大型 B 細胞淋巴瘤 (DLBCL) 病人。 本適應症係依據完全反應率(complete response rate)獲得加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 POLIVY in combination with bendamustine and rituximab is indicated for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for hematopoietic stem cell transplant. This indication is approved under accelerated approval based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
Posology	與 bendamustine 和 rituximab 併用，POLIVY 1.8 mg/kg 靜脈輸注 90 分鐘，每 21 天輸注一次，共 6 週期。 The recommended dose of POLIVY is 1.8 mg/kg as an intravenous infusion over 90 minutes every 21 days for 6 cycles in combination with bendamustine and a rituximab product.
Pharmacological Category **ATC Code**	L01XC37

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Polatuzumab vedotin, the drug substance (DS) of brand name POLIVY, is a conjugate of the two intermediates: polatuzumab antibody and a potent anti-mitotic agent, monomethyl auristatin E (MMAE).

Polatuzumab antibody intermediate (MCDS4409A)

Polatuzumab antibody, one of the intermediate of DS, is a humanized monoclonal antibody IgG1 that specifically recognizes human CD79b. The manufacturer of polatuzumab antibody is Genentech, USA.

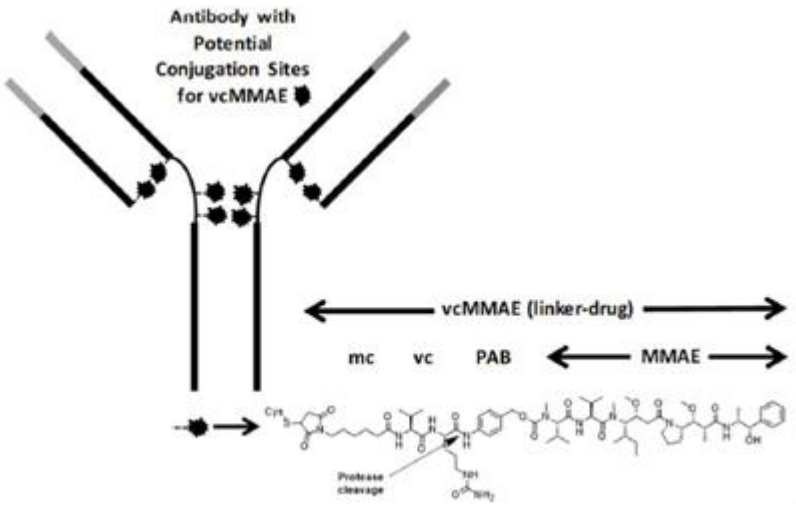
Polatuzumab antibody is produced in CHO cells and contains an N-linked glycan site at Asn297 in the C_H2 domain of the Fc portion of the molecule. The predominant glycosylation variants in polatuzumab antibody are asialo, agalacto biantennary structure with a core fucose (G0F) and one terminal (G1F) galactose residues. The calculated molecular mass of polatuzumab antibody is 145.0 kDa (peptide chains only). Detailed description of the origin, history and preparations of cell banks including MCBs, WCBs and EPCs are provided. Adventitious and endogenous agent safety testing, identity and genetic stability for cell banks were conducted based on the recommendations in ICH guidance. Raw materials of direct and indirect biological origin are also justified.

Characterization studies are presented including primary and higher-order structure, glycosylation, oxidation, disulfide structure, charge and size variants, and biological activity of target binding, as well as product variants and process-related impurities. The exclusion for some process-related impurities from routine testing is appropriately justified. Manufacturing process with in-process controls, process development histories for 3 process versions (tox, v0.1, and v1.0), comparability studies, process validation, specification, analytical methods and validation, batch analyses, reference materials and virus clearance studies, are provided abundantly to demonstrate the quality and consistency of polatuzumab antibody using commercial process.

Long-term (-20℃), accelerated (5℃), and stress (25℃/60% RH) stability studies have been carried out for polatuzumab antibody batches. The stability studies are derived from polatuzumab antibody batches produced with the commercial process.

Polatuzumab vedotin

The calculated molecular mass of polatuzumab vedotin is 149.6 kDa (without C-terminal lysines and without N-linked glycosylation). The manufacturer of polatuzumab vedotin is Lonza Ltd., Switzerland.



Characterization studies include primary and higher-order structure, post-translational modifications, conjugation sites, extent of MMAE derivative conjugation, charge and size variants, and biological activity analyzed by cell-based assay, as well as product variants and process-related impurities. The exclusion for some process-related impurities from routine testing is appropriately justified. Manufacturing process with in-process controls, process development histories, comparability studies, process validation, specification, analytical methods and validation, batch analyses, and reference materials, are provided to demonstrate the quality and consistency of polatuzumab vedotin.

Long-term (-20℃), accelerated (5℃), and stress (25℃/60% RH) stability studies have been carried out for polatuzumab vedotin commercial batches. The applicant commits to complete the long-term studies according to the proposed stability protocol.

2.1.2 Drug Product

POLIVY, 140 mg/vial polatuzumab vedotin, is provided in single-dose 20 mL vials as a sterile, white to grayish-white lyophilized cake and contains no preservatives. It is intended for intravenous infusion after reconstitution with SWFI and dilution in 0.9% sodium chloride solution, 0.45% sodium chloride solution, or 5% dextrose solution. The manufacturer for the drug product (DP), POLIVY, is BSP Pharmaceuticals S.p.A., Italy.

The composition of DP is listed. The excipients for DP are complied with USP-NF/Ph. Eur./JPE. No novel excipients are used in the formulation. Sucrose is the only excipient manufactured using materials (activated charcoal) of animal origin in DP. The manufacturing processes of activated charcoal meet the criteria defined in EMA/410/01.

DP manufacturing process and formulation development are described appropriately. Adequate justifications for potential impurities and the container closure integrity are provided to support the suitability of the container closure system. The compatibility data is submitted adequately. Manufacturing process within process controls, process validation,

specification and batch analyses are provided and show that the manufactures of POLIVY are controlled properly and consistently.

The release and stability specifications for POLIVY include appearance, general characteristic properties, quantity, identity, purity/impurity, potency and safety. The specifications of POLIVY are generally acceptable.

Stability studies, conducted under long-term storage (5℃), accelerated (25℃/60%RH) and stress (40℃/75% RH) conditions, and in-use stability studies could support the storage and on-site usage for POLIVY. The current data of long-term stability studies supports the shelf life of POLIVY for 18 months under the storage condition of 5℃, protected from light.

In conclusion, information on the intermediates, drug substance and finished drug product is regarded as appropriate to support the quality of POLIVY.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Polatuzumab vedotin is a CD79b-targeting antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent monomethyl auristatin E (MMAE) to B cells, which results in the killing of malignant B-cells. Polatuzumab vedotin induced antibody-dependent cell-mediated cytotoxicity (ADCC) with at least an order of magnitude lower activity than the positive control, while it did not induce complement dependent cytotoxicity (CDC). Polatuzumab vedotin demonstrated anti-proliferative activity in CD79b-positive cells but not CD79b- negative cells, while MMAE had the effects regardless of CD79b expression status, indicating CD79b targeting nature of polatuzumab vedotin.

Polatuzumab vedotin treatment showed significant anti-tumor activity in human B-cell lymphoma and DLBCL mouse xenograft models. The combination of polatuzumab vedotin with anti-CD20 monoclonal antibodies and CHP (cyclophosphamide, doxorubicin, and prednisone) or bendamustine chemotherapy demonstrated better efficacy than polatuzumab vedotin alone or the doublet of anti-CD20 antibodies (rituximab or obinutuzumab) plus chemotherapy. MMAE alone did not significantly inhibit the hERG channel *in vitro*. No polatuzumab vedotin -induced adverse effects on CNS, cardiovascular, or respiratory function were observed in monkeys.

2.2.2 Toxicological Studies

With repeated administration of polatuzumab vedotin or MMAE in rats or monkeys, or repeated administration of the surrogate ADC in monkeys, the principal test article-related effects in both species included the changes in the bone marrow and lymphoid tissues. In rats, but not monkeys, effects on the testis and liver were seen. With the exception of testes, the adverse findings were generally reversible and are the expected toxicities of a tubulin-binding agent. MMAE was positive in a rat micronucleus study. Non-reversible

testicular toxicity was observed in rats, which appeared to be related to the MMAE moiety. In an EFD study in pregnant rats, administration of two intravenous doses of MMAE (approximately 0.5-fold the human recommended dose, on AUC basis) on gestational days 6 and 13 caused embryo-fetal mortality and structural abnormalities. Based on findings from animal studies and its mechanism of action, polatuzumab vedotin can cause fetal harm.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

After the first dose of 1.8 mg/kg polatuzumab vedotin, the acMMAE mean (±SD) C_{max} was 803 (± 233) ng/mL and AUC_{inf} was 1860 (± 966) day•ng/mL; the unconjugated MMAE mean (±SD) C_{max} is 6.82 (±4.73) ng/mL and AUC_{inf} was 52.3 (± 18.0) day•ng/mL. The plasma exposure of acMMAE and unconjugated MMAE increased approximately dose proportionally over a polatuzumab vedotin dose range from 0.1 to 2.4 mg/kg (0.06 to 1.33 times the approved recommended dosage). Cycle 3 acMMAE AUC were predicted to increase by approximately 30% over Cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. Unconjugated MMAE plasma exposures were <3% of acMMAE exposures and the AUC and C_{max} were predicted to decrease after repeated every-3-week dosing.

The acMMAE central volume of distribution estimated based on population PK analysis is 3.15 L. For human, MMAE plasma protein binding is 71% to 77% and the blood to plasma ratio is 0.79 to 0.98, *in vitro*. Polatuzumab vedotin catabolism has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. MMAE is a substrate for CYP3A4.

The acMMAE terminal half-life is approximately 12 days (95% CI: 8.1 to 19.5 days) at Cycle 6 with predicted clearance of 0.9 L/day. The unconjugated MMAE terminal half-life is approximately 4 days after the first polatuzumab vedotin dose.

2.3.2 Interaction Studies

No dedicated clinical drug–drug interaction studies with POLIVY in humans have been conducted. *In vitro* study showed that MMAE is CYP3A and P-gp substrate.

PBPK modeling prediction result showed that concomitant use of polatuzumab vedotin with ketoconazole (strong CYP3A inhibitor) may increase unconjugated MMAE AUC by 45%. Concomitant use of polatuzumab vedotin with rifampin (strong CYP3A inducer) may decrease unconjugated MMAE AUC by 63%. Concomitant use of polatuzumab vedotin is predicted not to affect exposure to midazolam (a sensitive CYP3A substrate). Monitor patients for signs of toxicity when polatuzumab vedotin is used concomitantly with strong CYP3A inhibitors.

There are no clinically significant differences in the pharmacokinetics of acMMAE or unconjugated MMAE when polatuzumab vedotin is used concomitantly with bendamustine

or rituximab based on population PK modeling prediction.

2.3.3 Special Populations

No clinically significant differences in the PK of polatuzumab vedotin were observed based on age (20 to 89 years) or sex. No clinically significant differences in the PK of acMMAE or unconjugated MMAE were observed based on mild to moderate renal impairment. In mild hepatic impairment, there was a 40% increase in MMAE exposure, which was not deemed clinically significant. Therefore, no dose adjustment is recommended in patients with mild to moderate renal impairment or mild hepatic impairment.

The effect of severe renal impairment, end-stage renal disease with or without dialysis, moderate to severe hepatic impairment, or liver transplantation on the PK of acMMAE or unconjugated MMAE is unknown.

Across clinical trials, 14/536 (2.6%) evaluable polatuzumab vedotin-treated patients tested positive for such antibodies at one or more post-baseline time points. Due to the limited number of patients with antibodies against polatuzumab vedotin, no conclusions can be drawn concerning a potential effect of immunogenicity on PK.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One Phase Ib/II open-label Study [GO29365] of descriptive statistics was provided and evaluated for polatuzumab vedotin (POLIVY) in combination with bendamustine (B) and rituximab (R) or obinutuzumab (G) in patients age ≥18 years with relapsed or refractory (R/R) follicular lymphoma (FL) (Grade 1, 2, or 3a) or diffuse large B-cell lymphoma (DLBCL). Patients must have received at least one prior therapy for FL or DLBCL.

The study consisted of two stages, the Phase Ib Safety run-in stage and the Phase II randomized and expansion stage, run sequentially and separately in cohorts of patients with R/R FL and R/R DLBCL histology. The efficacy evaluation was mainly based on the phase II part of DLBCL patients. In this part, enrolled subjects were randomized 1:1 to receive polatuzumab vedotin 1.8mg/kg in combination with bendamustine and rituximab (BR) or BR alone, for up to six 21-day cycles.

The primary efficacy endpoint of complete response (CR) rate at the primary response assessment (6-8 weeks after Cycle 6 Day 1 or last dose of study medication) based on PET-CT as determined by the IRC in patients with R/R DLBCL in the Phase II randomized stage was higher in the polatuzumab vedotin + BR arm (40.0% [16/40 patients]; 95% CI: 24.9%, 56.7%) compared with the BR arm (17.5% [7/40 patients]; 95% CI: 7.3%, 32.8%).

The results of secondary and exploratory endpoints were described as below. For responders, the median duration of response (DoR) was 12.6 months in polatuzumab vedotin + BR arm and 7.7 months in the BR arm. The median PFS was 9.5 months in polatuzumab vedotin +

BR arm compared to 3.7 months in BR arm. The median OS was 12.4 months in polatuzumab vedotin + BR arm compared to 4.7 months in BR arm. Owing to the small sample size, the clinical robustness of PFS and OS is limited.

2.4.2 Safety Results

In study GO29365, patients treated with polatuzumab vedotin + BR with a median of 5 cycles, while patients treated with BR with a median of 3 cycles. Almost all subjects in this study experienced at least one AE (polatuzumab vedotin + BR: 100% vs. BR: 97%). There were 23% subjects who had fatal AE in polatuzumab vedotin + BR arm and 28% subjects who had fatal AEs in BR arm. In the randomized phase of study GO29365, 71.8% of patients treated with polatuzumab vedotin + BR needed any study drug treatment modification or interruption due to AEs, and 48.7% treated with BR needed any study drug treatment modification or interruption due to AEs.

Neutropenia, anemia, thrombocytopenia, diarrhea, and peripheral neuropathy AE were the most common AE in the polatuzumab vedotin + BR arm. Infections related AEs happened in both arms. Febrile neutropenia, pyrexia and pneumonia were the most common SAE in the polatuzumab vedotin + BR arm. The frequencies of febrile neutropenia, and infection were similar in two arms. No new safety signal was noted currently with lyophilized formulation of polatuzumab vedotin with BR.

2.5 Bridging Study Evaluation

Based on the NCA results from studies JO29138 and DCS4968g, after single dosing 1.8 mg/kg polatuzumab vedotin (pola), the acMMAE C_{max} and AUC_{inf} at Cycle 1 in Asian patients (N=3) was about 0.76-fold and 1.21-fold than in Non-Asian patients (N=6); the total antibody C_{max} and AUC_{inf} in Asian patients was about 1.45-fold and 2.45-fold than in Non-Asian patients; the MMAE C_{max} and AUC_{inf} in Asian patients was about 0.24-fold and 0.34-fold than in Non-Asian patients. For simulated PK exposure after 1.8 mg/kg polatuzumab vedotin Q3W by population PK modeling, the acMMAE C_{max} and AUC in Asian patients was about 1.00-fold and 0.99-fold than in Non-Asian patients; the MMAE C_{max} and AUC_{inf} in Asian patients was about 0.81-fold and 0.83-fold than in Non-Asian patients. However, only 3.9% Asian patients (N=18) was involved in this analysis. The inter-subject variation was about 29 to 52% for acMMAE and 34 to 69% for MMAE. The metabolism pathway of polatuzumab vedotin is catabolism, which is not considered affected by ethnicity.

Due to limited Asian PK data provided, the conclusion of whether ethnic difference existed or not could not be drawn from PK perspective.

Clinically, the ethnic difference was evaluated based on 10 subjects enrolled from South Korea in the pivotal study GO29365. Six of the 10 Korean received polatuzumab with bendamustine and rituximab. The efficacy (tumor response) of East Asian was similar to the

overall population. More events of myelosuppression and treatment discontinuation occurred in Asian than non-Asian subjects receiving polatuzumab vedotin + BR. All 6 Asian subjects in polatuzumab vedotin + BR arm had severe myelosuppression AE. Grade 5 AE occurred 33% in Asian (2 of the 6 Asian subjects died for pneumonia and hemoptysis) and 21% in non-Asian.

The small sample size of East Asian limited the evaluation for ethnic sensitivity from the perspective of PK, efficacy and safety. The ethnic sensitivity is unknown. Considering the unmet medical condition for relapse/refractory DLBCL, and the feasibility of clinical monitor as well as management for myelosuppression, the bridging study was considered waived conditionally. The sponsor should provide Japanese data in study JO40762 after its completion. Besides, Taiwanese data can be used as supportive information for evaluating ethnic sensitivity. Therefore, Taiwanese data is also recommended to be collected and reported in study GO39942.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. Generally, the overall benefit-risk assessment of POLIVY (Polatuzumab vedotin) was favorable for relapse/refractory DLBCL patients who are not candidates for hematopoietic stem cell transplant. The efficacy evidence was mainly based on the complete response rate in pivotal trial GO39365, and complete response is considered a potential surrogate endpoint which is reasonably likely to predict a clinical benefit. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure that the benefits of the drug outweigh the risks.

In conclusion, the overall benefit/risk ratio is favorable to support accelerated approval for the indication as below:

POLIVY in combination with bendamustine and rituximab is indicated for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for hematopoietic stem cell transplant.

Ongoing phase III study GO39942 or study MO40598 would be served as the confirmatory trials.

3. Post-Marketing Requirements

(1) Complete study GO39942 and provide its final CSR.
(2) Complete study MO40598 and provide its final CSR.
(3) Provide Japanese data in study JO40762 after completion of the studie.
(4) Develop and validate the assay to evaluate the neutralizing antibody, and provide the final report.