Taiwan Food and Drug Administration

Assessment Report

Trade Name：威絡益凍晶注射劑 100 毫克/VYLOY Powder for concentrate for solution for infusion 100 mg

Active Ingredient：zolbetuximab

License Number：MOHW-BI 001278

Applicant：台灣安斯泰來製藥股份有限公司

Approval Date：2025/01/20

Indication：
與含氟嘧啶(fluoropyrimidine)和含鉑的化學治療併用，適用於Claudin (CLDN) 18.2 陽性、第二型人類表皮生長因子受體(HER2)陰性的局部晚期不可切除或轉移性胃腺癌或胃食道接合處(GEJ)腺癌成人病人的第一線治療。

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive

Background Information

Trade Name	威絡益凍晶注射劑 100 毫克 / VYLOY Powder for concentrate for solution for infusion 100 mg
Active Ingredient(s)	zolbetuximab
Applicant	台灣安斯泰來製藥股份有限公司
Dosage Form & Strengths	凍晶注射劑 100mg
Indication	與含氟嘧啶(fluoropyrimidine)和含鉑的化學治療併用，適用於 Claudin (CLDN) 18.2 陽性、第二型人類表皮生長因子受體(HER2)陰性的局部晚期不可切除或轉移性胃腺癌或胃食道接合處(GEJ)腺癌成人病人的第一線治療。
Posology	請參閱仿單
Pharmacological Category **ATC Code**	L01FX31

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

General information

Zolbetuximab is a recombinant chimeric monoclonal antibody, binding to claudin-18 splice variant 2 (CLDN18.2) on the surface of target cells, initiating antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), which are mediated by the Fc region of the monoclonal antibody.

Manufacture

Zolbetuximab is produced using a recombinant CHO cell line. A flow diagram outlining the manufacturing process has been provided, along with detailed specifications for the process steps, including corresponding process controls, operating ranges, and action limits. The sponsor has also described, in sufficient detail, the preparation and testing of cell banks, the testing and acceptance criteria for raw materials, and the generation of the cell substrate. Process validation studies, including column and membrane lifetimes, hold times, and shipping conditions, have been completed. Comparability studies demonstrated that batches produced using different manufacturing processes showed no significant changes in the tested quality attributes.

Characterization

The primary structure and higher-order structure of Zolbetuximab, along with product- and process-related impurities and degradation profiles from stability studies, have been demonstrated.

Control of DS

The specifications for the drug substance (DS) have been provided, and the acceptance criteria have been appropriately justified. All batch results met the established criteria, demonstrating consistency in DS quality. Additionally, the Certificate of Analysis (CoA) for the bulk drug substance confirms that all test results comply with the specification criteria. Furthermore, a leachable and extractable study has been conducted to assess potential toxicological risks.

Stability

A shelf life for the drug substance is proposed at -70°C ± 10°C under long-term storage conditions. The long-term stability study includes test results from three primary batches and one supportive batch, all of which fall within the acceptance

range. Stability studies under accelerated and stressed conditions have also been completed.

2.1.2 Drug Product

Description of DP

Zolbetuximab drug product (DP) is a sterile, preservative-free, white to off-white lyophilized powder provided in a single-dose vial. It is intended for intravenous infusion and is packaged in a Type I glass vial with a stopper and seal, topped with a flip-off cap. The quantitative composition, function, and quality standards of each component in the finished DP are specified. Overfills are applied to ensure the nominal volume can be accurately withdrawn from each vial.

Pharmaceutical Development

The composition of zolbetuximab commercial drug product (DP), developed in alignment with the commercial manufacturing process, ensures a stable product that meets the requirements for formulation, dose presentation, and shelf life.The drug product manufacturing process was initially established at Baxter Oncology Gmbh. During manufacturing process development, the sponsor provided a comparative overview of the drug product manufacturing processes at key development stages. Comparability studies were conducted to support these changes, with the scope determined by the level of risk associated with each modification.

For microbiological attributes, the zolbetuximab formulation does not contain an antimicrobial preservative. Microbial control is ensured through in-process controls and batch release testing.

In-use stability studies were conducted to evaluate the physicochemical compatibility of the product with the diluent and medical apparatus materials, as well as the potential for microbial growth, ensuring suitability under the proposed preparation and administration conditions.

Control of DP

The specifications for DP are provided, and the acceptance criteria are justified. Test results at release meet the acceptance criteria. Certificates of Analysis (CoA) for DP batches are provided.

Stability

A shelf life for the drug product is proposed at 5 °C ± 3 °C under long-term storage

conditions. The long-term stability study includes test results from three PPQ batches, all of which fall within the acceptance range. Stability studies under accelerated and stressed conditions are also completed.

Overall, the sponsor has provided sufficient information regarding the general properties of DS, manufacturing processes for the active substance and finished product, raw materials, controls for DS and DP, and stability studies of DS and DP. Therefore, the quality of this product is considered to be acceptable. Physicochemical and biological aspects have been investigated and are controlled in a satisfactory way.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The pharmacological profile of zolbetuximab has been well-characterized through a series of studies addressing its target binding, mechanism of action, tissue selectivity, and antitumor efficacy. Zolbetuximab exhibited comparable binding affinities to human, mouse, and cynomolgus monkey CLDN18.2. Chemotherapy regimens (FLO or EOF) enhanced zolbetuximab's target binding. Zolbetuximab induced antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in CLDN18.2-positive cell lines but not in CLDN18.2-negative cells or those expressing CLDN18.1. Chemotherapy regimens further enhanced its ADCC and CDC activity. In immunocompetent mice, zolbetuximab combined with EOF or OF significantly improved tumor inhibition, CD8+ T-cell infiltration, and survival compared to zolbetuximab monotherapy or EOF/OF alone. Tissue selectivity studies confirmed zolbetuximab's enrichment in CLDN18.2-positive tumors. Safety pharmacology studies in mice and monkeys revealed no test article-related effects on the central nervous system, cardiovascular system, or respiratory system.

2.2.2 Toxicological Studies

Single- and repeated-dose toxicity studies demonstrated no significant toxicities, and acceptable safety margins were established based on AUC comparisons. In the repeated-dose study, minor non-severe vomiting was observed in cynomolgus monkeys, with no other adverse findings. The NOAELs provide safety margins of 8.6-fold in mice and 8-fold in monkeys relative to the clinical dose of 300 mg/kg. Zolbetuximab did not undergo genotoxicity or carcinogenicity studies, consistent with ICH S6(R1) and ICH S9. An EFD study in mice demonstrated that zolbetuximab could cross the placental barrier, with no discernible embryo-fetal toxicities. However, in a literature reference, a potential risk of postnatal atrophic gastritis was revealed by CLDN18.2 knockout mice. Investigations into clinical observations of nausea and vomiting revealed that zolbetuximab-induced emesis in ferrets correlated with histopathological damage to gastric mucosa expressing CLDN18.2.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Zolbetuximab is administered by IV infusion, resulting in 100% bioavailability. Based on the Population PK (PopPK) analysis, the mean total volume of distribution at steady state was estimated to be 16.4 L. The estimated clearance and mean $t_{1/2}$ of zolbetuximab were 0.0150 L/h and 43.6 days, respectively, indicating the low clearance rate of zolbetuximab. Following single dose administration, zolbetuximab exhibited dose-proportional PK at doses ranging from 33 to 1000 mg/m^2. The dose-proportionality of zolbetuximab at steady-state was also observed across doses 600 to 1000 mg/m^2 Q3W.

The proposed dose of zolbetuximab is 800 mg/m^2 for the loading dose followed by 600 mg/m^2 Q3W, or 400 mg/m^2 Q2W. A loading dose of 800 mg/m^2 was used to reach the effective concentration values, and maintenance dose regimen 600 mg/m^2 Q3W (Q3WBSA regimen) was used in pivotal clinical studies and for commercial based on the low elimination rate and mild accumulation factor (1.53 for AUC dosed with 3-week interval) of zolbetuximab. Furthermore, 400 mg/m^2 Q2W (Q2WBSA regimen) was another proposed maintenance dose regimen of zolbetuximab. In PopPK model, the differences in zolbetuximab exposure of Q3WBSA and Q2WBSA regimens were not considered as clinically meaningful, and there was no difference in C_{ave} throughout the treatment period between the 2 regimens. Therefore, the efficacy and safety profile will also likely be similar between the two dose regimen.

2.3.2 Interaction Studies

Zolbetuximab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways, hence it is not expected to be metabolized by the cytochrome P450 enzymes or perform drug-drug interactions. In Study ILUSTRO, the magnitude of drug-drug interactions between zolbetuximab and mFOLFOX6 regimen was not considered clinically meaningful. No dose adjustment is required for zolbetuximab and mFOLFOX6 when used in combination.

2.3.3 Special Populations

In Pop-PK model, the differences of zolbetuximab exposure metrics were not considered clinically meaningful by age (22 to 83 years), gender (37.7% female), race (50.1% white, 42.2% Asian, 0.8% black, 6.9% other or missing), albumin (21.0 to 72.4 g/L), sum of tumor diameter (10.0 to 400.0 mm), renal function with Cockcroft-Gault creatinine clearance (21.9 to 210.9 mL/min), hepatic function based on NCI-ODWG Criteria (84.3% normal, 15.1% mild, 0.6% moderate), or cancer type (75.6% stomach, 24.4% GEJ). Gastrectomy status (31.5% conducted) was predicted to increase C_{ave} by

36.1% and C_{trough} by > 40%. Because the increase in zolbetuximab C_{ave} or C_{trough} was not expected to increase the safety risk of zolbetuximab, no dose adjustment is required.

Zolbetuximab systemic clearance, inter-compartmental clearance and the volume of distribution increased with increasing BSA. However, the magnitude of the covariate effect on exposure metrics was not considered clinically meaningful in PopPK model. Exploratory analyses were also conducted to compare the fixed dosing regimens Q3WFIX (1400/1000 mg Q3W) and Q2WFIX (1400/700 mg Q2W) with the proposed BSA-normalized dosing regimen Q3WBSA. The results indicated that the fixed dosing regimens would have higher variabilities in drug exposure across different BSA quartiles, which supported the BSA-normalized dosing for zolbetuximab.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two almost identically designed Phase III, randomized, double-blind studies in participants with CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma, had demonstrated superior progression-free survival (PFS) time of zolbetuximab plus mFOLFOX6 to mFOLFOX6 alone in Study 8951-CL-0301 (SPOTLIGHT) (median: 10.61 vs. 8.67 months; HR (95% CI): 0.751 (0.598, 0.942); 1-sided p=0.0066 (stratified log-rank test)) and of zolbetuximab plus CAPOX to CAPOX alone in Study 8951-CL-0302 (GLOW) (median: 8.21 vs. 6.80 months; HR (95% CI): 0.687 (0.544, 0.866); 1-sided p=0.0007 (stratified log-rank test)).

At the final PFS analysis, the interim analysis of the overall survival (OS) also showed a statistically significant benefit (to 1-sided significance level of 0.0135) of zolbetuximab plus mFOLFOX6 to mFOLFOX6 alone in Study 8951-CL-0301 (SPOTLIGHT) (median: 18.23 vs. 15.54 months; HR (95% CI): 0.750 (0.601, 0.936); 1-sided p=0.0053 (stratified log-rank test)) and of zolbetuximab plus CAPOX to CAPOX alone in Study 8951-CL-0302 (GLOW) (median: 14.39 vs. 12.16 months; HR (95% CI): 0.771 (0.615, 0.965); 1-sided p=0.0118 (stratified log-rank test)).

2.4.2 Safety Results

The overall safety evaluation was based on the two phase 3 studies and two phase 2 studies 8951-CL-0103 (ILUSTRO) and GM-IMAB-001-03 (FAST), that included 631 subjects who received zolbetuximab in combination with mFOLFOX6, CAPOX or EOX (epirubicin, oxaliplatin, and capecitabine) and 611 subjects who received placebo in combination with mFOLFOX6, CAPOX or EOX. The regimen of zolbetuximab was an 800 mg/m^2 loading dose followed by 600 mg/m^2 Q3W.

The incidence of any treatment-emergent adverse event (TEAE), Grade ≥ 3 TEAE, or serious TEAE was comparable between the zolbetuximab group and the placebo group. However, the incidence of TEAEs leading to treatment discontinuation or interruption was high in the zolbetuximab group compared to the placebo group.

Among the TEAEs occurring in ≥ 10% of subjects in the zolbetuximab group, nausea (77.0% vs. 58.6%), vomiting (66.9% vs. 36.2%), decreased appetite (41.2% vs. 31.9%), hypoalbuminemia (16.6% vs. 9.2%), and edema peripheral (13.5% vs. 6.1%) were reported with a ≥ 5% higher incidence in the zolbetuximab group than in the placebo group.

Among the Grade ≥ 3 TEAEs occurring in ≥ 5% of subjects in the zolbetuximab group, neutropenia (20.1% vs. 14.6%), vomiting (13.6% vs. 4.6%), nausea (11.6% vs. 4.6%), and decreased appetite (5.4% vs. 2.3%) were reported with a ≥ 3% higher incidence in the zolbetuximab group than in the placebo group.

The most commonly reported TEAE leading to death was malignant neoplasm progression (2.5% vs. 5.2%).

Among the serious TEAEs occurring in ≥ 2% of subjects in the zolbetuximab group, vomiting (6.7% vs. 3.9%) and nausea (4.9% vs. 3.1%) were reported with a ≥ 1% higher incidence in the zolbetuximab group than in the placebo group.

Among the TEAEs leading to discontinuation of any study drug occurring in ≥ 2% of subjects in the zolbetuximab group, nausea (5.9% vs. 1.1%) and vomiting (5.4% vs. 1.1%) were reported with a ≥ 1% higher incidence in the zolbetuximab group than in the placebo group. Vomiting (3.8% vs. 0.5%) and nausea (3.3% vs. 0.3%) were also the most common TEAEs leading to discontinuation of zolbetuximab or placebo with a ≥ 1% higher incidence in the zolbetuximab group than in the placebo group.

Among the TEAEs leading to interruption of zolbetuximab or placebo occurring in ≥ 5% of subjects in the zolbetuximab group, vomiting (26.5% vs. 1.5%) and nausea (25.4% vs. 0.7%) and vomiting (5.4% vs. 1.1%) were reported with a ≥ 3% higher incidence in the zolbetuximab group than in the placebo group.

The group term “Hypersensitivity Reactions” was reported in 33.8% subjects in the zolbetuximab group and 29.8% in the placebo group. Grade ≥ 3 “Hypersensitivity Reactions” events were reported in 4.6% in the zolbetuximab group and 2.1% in the placebo group.

The group term “Infusion-related Reactions (IRRs)” were reported in 36.1% subjects in the zolbetuximab group and 9.5% in the placebo group. Grade ≥ 3 “IRRs” events were reported in 6.3% in the zolbetuximab group and 0.5% in the placebo group. Anaphylactic reaction occurred in 0.5% subjects in both groups.

2.5 Bridging Study Evaluation

The difference of zolbetuximab pharmacokinetic parameters were not considered clinically meaningful across the Chinese subjects in Study 8951-CL-0105, the Japanese subjects in Study 8951-CL-0104, and the White subjects in Study ILUSTRO. Additionally, the simulated zolbetuximab pharmacokinetic parameters and concentration-time profiles following 800/600 mg/m^2 Q3W regimen were also comparable between White and East Asian subjects.

The two pivotal clinical studies enrolled 177 (31.3%, SPOTLIGHT) and 257 (50.7%, GLOW) subjects from East Asia (China, Japan, South Korea, and Taiwan), respectively. The efficacy results were better for the East Asian population compared to non-East Asian population. The safety results were generally comparable between the two population.

The bridging study was waived based on the above pharmacokinetic and clinical data.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team recommends approval of zolbetuximab.

1. Recommended indication:

   In combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are Claudin (CLDN) 18.2 positive.

2. The recommended dose:

   - First loading dose: 800 mg/m^2 intravenously
   - Subsequent maintenance doses:
     - 600 mg/m^2 intravenously every 3 weeks, or
     - 400 mg/m^2 intravenously every 2 weeks

   Continue treatment until disease progression or unacceptable toxicity

3. Post-Marketing Requirements

Nil