Taiwan Food and Drug Administration

Assessment Report

Trade Name：芮寶興凍晶注射劑/
Reblozyl powder for solution for injection

Active Ingredient：Luspatercept

License Number：MOHW-BI 001201

Applicant：台灣必治妥施貴寶股份有限公司

Approval Date：111.11.10

Indication：用於治療 IPSS-R 分級為非常低度至中度風險(very low to intermediate risk) 且具有 ring sideroblasts 之骨髓增生不良症候群(myelodysplastic syndrome)所導致的輸血依賴型貧血成人病人，病人需對紅血球生成素基礎療法(erythropoietin-based therapy)治療效果不佳或是不適用紅血球生成素基礎療法。

The treatment of adult patients with transfusion-dependent anemia due to IPSS-R very low, low, and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.

Background Information

Trade Name	芮寶興凍晶注射劑 / Reblozyl powder for solution for injection
Active Ingredient(s)	Luspatercept
Applicant	台灣必治妥施貴寶股份有限公司
Dosage Form & Strengths	凍晶注射劑/ 25 毫克和 75 毫克
Indication	用於治療 IPSS-R 分級為非常低度至中度風險(very low to intermediate risk) 且具有 ring sideroblasts 之骨髓增生不良症候群(myelodysplastic syndrome)所導致的輸血依賴型貧血成人病人，病人需對紅血球生成素基礎療法(erythropoietin-based therapy)治療效果不佳或是不適用紅血球生成素基礎療法。
Posology	詳見仿單。
Pharmacological Category **ATC Code**	B03XA06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Luspatercept is a recombinant Fc fusion protein consisting of the modified extracellular domain (ECD) of human activin receptor IIB (ActRIIB) linked to the human IgG1 Fc domain. Luspatercept has special design in the ligand binding domain which significantly reduces binding to activin A but maintains binding to other ligands such as growth differentiation factor 11 (GDF-11) and activin B, albeit at a lower level. The mechanism of action of Luspatercept is based on binding to a soluble target, GDF-11, without involvement of the Fc region effector functions.

Luspatercept is produced by cultivation of recombinant CHO cells and has a molecular mass of 94 kDa for the major glycoform. Detailed description of the origin, history and preparations of cell banks including MCBs, WCBs and EPCs are provided. Adventitious and endogenous agent safety testing and identity 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. Manufacturing process with in-process controls, process development histories, 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 Luspatercept using commercial process.

Long-term (<-65°C), accelerated, and stress stability studies have been carried out for Luspatercept DS batches. The stability studies are derived from Luspatercept DS batches produced with the commercial process.

2.1.2 Drug product

Reblozyl is formulated as a single-use, sterile, preservative-free, lyophilized powder intended for subcutaneous administration after reconstitution with sterile water for injection (WFI). The bulk solution is compounded at 50 mg/mL. The drug product is available in two presentations, 25 mg/vial and 75 mg/vial. Reblozyl is manufactured at Patheon Italia S.p.A., Italy.

The composition of DP is listed. The excipients for DP are complied with USP-NF, Ph. Eur., and JP compendia specifications. There are no novel excipients in the DP. No excipients of human or animal origin are used in the DP.

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 Reblozyl are controlled properly and consistently.

The release specification and stability specification for Reblozyl include appearance, general characteristic properties, quantity, identity, purity/impurity, potency by cell-based bioassay and safety. The specifications of Reblozyl are generally acceptable.

The current data of long-term stability studies supports the shelf life of Reblozyl for 18 months under the storage condition of 5±3°C.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Luspatercept is a recombinant fusion protein derived from human activin receptor type IIb (ActRIIb) linked to an IgG1 Fc domain. It selectively binds TGF-β superfamily ligands to

reduce Smad 2/3 signaling that is abnormally high in the bone marrow of patients with myelodysplastic syndromes and β-thalassemia. The pharmacology studies were conducted with luspatercept or its murine orthologous protein, RAP-536, to investigate the effects. The *in vitro* pharmacology studies confirmed the binding affinity and determined the ability of luspatercept to inhibit Smad 2/3 signaling.

The results of the *in vivo* pharmacology studies indicated that luspatercept induced a significant and dose-dependent increase in RBC count, hemoglobin, and hematocrit in normal animals. Luspatercept also induced a more rapid recovery in some animal models of anemia. In the erythroid progenitor populations, luspatercept decreased basophilic erythroblasts and increased later-stage poly/orthochromatic erythroblasts, which indicated that luspatercept stimulated erythroid maturation. The combination of luspatercept and EPO resulted in a greater increase in hematological parameters than the single treatment alone. Although the effects of luspatercept on erythropoiesis are independent of EPO, EPO is still required to sustain erythropoiesis over the long term. In the MDS transgenic mouse model, administration of 10 mg/kg RAP-536 SC BIW increased RBC count, hemoglobin, and hematocrit. The safety pharmacology was evaluated in the toxicity studies, and there were no luspatercept-related findings in parameters of CNS, cardiovascular, and respiratory systems observed.

2.2.2 Toxicological Studies

The pivotal toxicity studies were conducted in rats (up to 13 weeks) and monkeys (up to 6 months). NOAEL could not be determined in most studies because the adverse findings occurred in the low-dose group. The major toxicological target organ was the kidney which presented membranoproliferative glomerulonephritis. In the reproductive and developmental toxicity studies, luspatercept might affect the female reproductive function and fetal development. The juvenile toxicity study demonstrated that the target organs and responses of luspatercept were similar between young and adult animals. The carcinogenicity study was not conducted, but three hematologic malignancies were observed in the juvenile toxicity study. Since these tumors only presented in the high-dose group and were unusual in the juvenile animals, the carcinogenicity of luspatercept was still uncertain.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Luspatercept was slowly absorbed following subcutaneous administration in patients, with the serum T_{max} at 7 days post-dose across all dose levels. The luspatercept C_{max} and AUC in serum approximately increased in a dose proportional manner in a dose range from 0.125 to 1.75 mg/kg, and the absorption was not significantly affected by the injection sites (upper arm, thigh or abdomen). When administered every three weeks, luspatercept serum concentration reaches the steady state after 3 doses, with an accumulation ratio of approximately 1.5.

The mean apparent volume distribution and total clearance were 9.68 L and 0.516 L/day for patients with myelodysplastic syndromes (MDS), respectively. Due to the large molecular mass, luspatercept distributed primarily in extracellular fluids and was not expected to be excreted into urine. It was also expected to be catabolized by general protein degradation process.

Following luspatercept treatment, the greatest mean hemoglobin (Hb) increase was observed after the first dose, with additional smaller increases after subsequent doses. Hb levels returned to baseline approximately 6-8 weeks from the last dose. Increasing luspatercept AUC was associated with a greater Hb increase in MDS patients with lower baseline RBC transfusion burden.

2.3.2 Interaction Studies

PopPK analysis revealed that concurrent iron chelation therapy had no significant effect on luspatercept PK.

2.3.3 Special Populations

No dose adjustment of starting dose was recommended for elderly population, mild to severe hepatic impaired population (NCI-ODWG classification) and mild to moderate renal impaired population. PK data was not available for patients with liver enzymes (ALT or AST) $\geqq$ 3x ULN, severe renal impairment (eGFR<30 mL/min/1.73m^2) and ESRD.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Applicant provided a pivotal study, MEDALIST (Protocol number: ACE-536-MDS-001), to claim the efficacy of Luspatercept (ACE-536) for the treatment of anemia in lower (very low, low, or intermediate) IPSS-R risk MDS-RS subjects who require RBC transfusions.

When comparing efficacy of primary endpoint, proportions of red blood cell-transfusion independence (RBC-TI) $\geq$ 8 weeks with duration of week 1-24 for luspatercept and placebo groups were 37.91% and 13.16%, respectively ($p < 0.0001$). Superiorities of the two key secondary endpoints, RBC-TI $\geq$ 12 weeks with duration of week 1-48 and RBC-TI $\geq$ 12 weeks with duration of week 1-24, were also demonstrated significantly. Subgroup and supportive analyses coincided with the main analyses results.

Therefore, it is statistically evidential for the applicant to claim the efficacy of Luspatercept (ACE-536) for the treatment of anemia in lower IPSS-R risk MDS-RS subjects who require

RBC transfusions.

2.4.2 Safety Results

In Study ACE-536-MDS-001, the mean and median treatment durations were 76.7 weeks and 50.9 weeks in the luspatercept arm comparing to 31.7 weeks and 24.0 weeks in the placebo arm. Consistent with the longer treatment duration for subjects in the luspatercept arm, the incidence of Grade 3 or 4 adverse events (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation, and AEs leading to dose interruption or reduction was higher in the luspatercept arm versus the placebo arm. The exposure-adjusted incidence rate of Grade 3 or 4 AEs and SAEs were lower in the luspatercept arm compared to the placebo arm.

The most common adverse reactions were fatigue, diarrhea, asthenia, nausea, dizziness, back pain and headache. The most commonly reported Grade ≥ 3 adverse reactions were fatigue, syncope, hypertension, and asthenia. The most commonly reported SAEs were urinary tract infection, back pain, syncope and fall.

AEs of special interest included malignancy, embolic and thrombotic events, kidney injury, hypertension, hypersensitivity reactions, and musculoskeletal disorders. Unlike β-thalassemia, the incidence of hypertension was similar between the two treatment groups in MDS. There was no increased risk for progression to high-risk MDS or AML with luspatercept administration according to current evidence. However, the risk of malignancy associated with luspatercept requires long-term follow-up considering its mechanism of action and pre-clinical data.

2.5 Bridging Study Evaluation

No East Asian subjects were enrolled in MDS studies. The PK comparison among Taiwanese (n=10), non-East-Asians (n=72) and White population were evaluated in patients with β-thalassemia, resulting no significant difference among races. Considering the PK characteristics was similar between patients with β-thalassemia and MDS, the low potential of ethnic sensitivity could be extrapolated to population with MDS.

The clinical bridging study evaluation (BSE) were based on extrapolation from Study ACE-536-B-THAL-001 that supported the luspatercept approval for patients with β-thalassemia in Taiwan. Ongoing global Study ACE-536-MDS-002 designed to compare the efficacy and safety of luspatercept versus EPO in ESAs-naïve lower-risk MDS patients enrolled subjects in Japan, Korea and Taiwan. This study will provide clinical data from Asian subjects.

2.6 Conclusion

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

luspatercept.

The recommended indication is “The treatment of adult patients with transfusion-dependent anemia due to IPSS-R very low, low, and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.”.

The recommended initial dose is “1.0 mg/kg once every 3 weeks”. The dose has to be adjusted according to response and toxicity. The recommended maximum dose is “1.75 mg/kg once every 3 weeks”, and the recommended minimum dose is “0.8 kg/kg once every 3 weeks”.

3. Post-Marketing Requirements

1. As the requirement of EMA Risk Management Plan, submit the interim and final clinical study report of ACE-536-LTFU-001.
2. Submit the clinical study report of ACE-536-MDS-002, including the subgroup analyses for efficacy and safety in East Asian subjects, once available.
3. Submit the required report according to the “Pediatric and Rare Severe Disease Designation”.