Taiwan Food and Drug Administration

Assessment Report

Trade Name：異可適注射劑 / EBGLYSS Injection

Active Ingredient：Lebrikizumab

License Number：MOHW-BI 001265

Applicant：台灣禮來股份有限公司

Approval Date：2024.08.16

Indication：

異位性皮膚炎

適用於治療患有中度至重度異位性皮膚炎，且無法透過外用療法適當控制疾病或不建議接受這些療法之12歲以上且體重至少40公斤病人。可併用或不併用外用皮質類固醇治療。

Atopic Dermatitis

Indicated for the treatment of patients aged 12 years and older, weighing at least 40 kg, with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not advisable. EBGLYSS can be used with or without topical corticosteroids

1. Background Information

Trade Name	異可適注射劑 / EBGLYSS Injection
Active Ingredient(s)	Lebrikizumab
Applicant	台灣禮來股份有限公司
Dosage Form & Strengths	注射劑 250 mg/2 mL
Indication	異位性皮膚炎 適用於治療患有中度至重度異位性皮膚炎，且無法透過外用療法適當控制疾病或不建議接受這些療法之 12 歲以上且體重至少 40 公斤病人。可併用或不併用外用皮質類固醇治療。
Posology	請參見仿單。
Pharmacological Category **ATC Code**	D11AH10

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

Lebrikizumab is an immunoglobin G4 monoclonal antibody that binds with high affinity to interleukin (IL)-13 and selectively inhibits IL-13 signaling through the IL-4 receptor alpha (IL-4Rα)/ IL-13 receptor alpha 1(IL-13Rα1) pathway, thereby blocking the downstream effects of IL-13. Lebrikizumab-bound IL-13 can still bind IL-13Rα2, allowing subsequent internalization and natural clearance of IL-13. Blockade of IL-13 signaling is expected to be of benefit in diseases in which IL-13 is a key contributor to the disease pathogenesis.

2.1.1.1 Manufacture

The manufacturing process has been adequately described. Lebrikizumab is produced in Chinese Hamster Ovary cells. The upstream process includes cell expansion and harvesting, while the downstream process involves purification and formulation.

A thorough overview of critical in-process controls including in-process tests and process parameters along with their acceptance criteria has been provided.

Information on raw materials used in the manufacturing process has been adequately provided. Acceptable information has been provided regarding the manufacture and testing of the cell banks. The testing includes confirmation of the purity, identity and suitability of the cell banks for manufacturing use.

The manufacturing process has been validated to ensure it consistently produces

lebrikizumab drug substance with the intended quality.

2.1.1.2 Characterization

Lebrikizumab has been sufficiently characterized using physicochemical, biophysical and biological methods.

The product-related impurities/substances and process-related impurities have been identified and assessed.

2.1.1.3 Specifications

The drug substance specifications for lebrikizumab at release and for stability assessment have been provided. As requested, the applicant has tightened the specification acceptance criteria for several quality attributes. The proposed specification limits reflect the clinical experience and are considered acceptable.

2.1.1.4 Reference Materials

A two-tiered reference standard system has been established. Adequate information on the reference standards has been provided.

2.1.1.5 Stability

The stability data provided are adequate to support the proposed shelf-life for lebrikizumab drug substance when stored at the long-term storage condition in the proposed container.

2.1.1.6 Adventitious Agents

Viral safety has been confirmed through extensive testing and viral clearance studies. No materials of animal or human origin are used in the drug substance manufacturing process. Based on the data provided, the risk of transmission of TSE is considered negligible.

2.1.2 Drug Product

Lebrikizumab drug product, Ebglyss, is presented as a 250 mg/2 mL sterile solution for injection for subcutaneous administration. The drug product is contained in a 2.25 mL, Type I borosilicate glass syringe barrel with extra small round flange, 27G special thin wall x 8 mm staked needle, and closed with a rigid needle shield and a barrier film laminated elastomeric plunger. The semi-finished syringe described above is assembled with device components to form the autoinjector /pre-filled pen presentation. The excipients are L-histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injection. All excipients comply with the applicable compendial standards.

2.1.2.1 Manufacture

An adequate description of the manufacturing process and process controls has been

provided. The manufacturing process includes steps such as thawing, mixing, filtration, filling, and assembly. The manufacturing process has been validated. It has been demonstrated that the manufacturing process consistently produces a product that meets predefined quality criteria.

2.1.2.2 Specifications

The specifications for Ebglyss at release and for stability assessment have been provided. As requested, the applicant has tightened the specification acceptance criteria for several quality attributes. The proposed specification limits reflect the clinical experience and are considered acceptable.

2.1.2.3 Container Closure System

Adequate information on the container closure system used for Ebglyss has been provided. The container closure system was chosen based on studies proving its suitability for use with lebrikizumab injection in the delivery devices.

2.1.2.4 Stability

The stability data provided are adequate to support the proposed shelf-life of 24 months for Ebglyss when stored in the original carton protected from light at 2°C-8°C with a patient use period of 7 days stored up to 30°C.

In summary, information on lebrikizumab drug substance and lebrikizumab drug product has been adequately provided.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacology studies demonstrated that lebrikizumab and its parental murine antibody specifically targeted human IL-13 but did not bind to human IL-4. Lebrikizumab showed high binding affinity to human and cynomolgus monkey IL-13 and inhibited IL-13-induced phosphorylation of STAT6, the primary downstream signaling mediator of the IL-13Rα1/IL-4Rα receptor complex, while not affecting the binding of IL-13 to IL-13Rα1 or IL-13Rα2. Lebrikizumab exhibited dose-dependent inhibitory effects on IL-13-induced proliferation of Hodgkin lymphoma cells.

In an *in vivo* mouse airway inflammation model, lebrikizumab reduced human IL-13-induced inflammatory reactions, including the recruitment of inflammatory cells and eosinophils, IL-13Rα2 expression in the lung, and TGF- β1 levels in bronchoalveolar lavage fluid.

2.2.2 Toxicological Studies

GLP-compliant repeated-dose studies of 6 weeks, 13 weeks, and 9 months were conducted in cynomolgus monkeys, with the highest dose being 25 mg/kg of lebrikizumab administered once weekly by bolus IV or SC injection. Both injection methods showed good tolerability with no adverse findings and no significant changes in peripheral blood immunophenotype.

At the 9-month necropsy, absolute and relative uterine weights were uniformly lower in lebrikizumab dose groups compared to the control group; however, no microscopic abnormalities of the uterus were found at either the 3- or 9-month necropsy. No differences in uterine weights in a subsequent 9-month IV study in mature female monkeys which suggests that variability in sexual maturity could have contributed to the observed differences. The NOAELs for both SC or IV treatments were 25 mg/kg/week.

In embryo-fetal development, no maternal toxicity, embryo-fetal toxicity, or teratogenicity was observed; the NOAELs were 150/50 mg/kg (loading/maintenance dose) for both maternal toxicity and developmental endpoints. Seven monkeys in the lebrikizumab treatment groups tested ADA-positive. In prenatal and postnatal development, no treatment-related changes were observed in physical or functional development parameters, and no histopathology observations were noted during the terminal necropsy of infants.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following the 500 mg loading doses of EBGLYSS™ at Week 0 and Week 2, steady-state serum concentrations were achieved with the first 250 mg Q2W dose at Week 4. Based on a population pharmacokinetic (PK) analysis at Week 16, The $C_{max,ss}$, the $C_{avg,ss}$, and the $C_{trough,ss}$ following the 250 mg Q2W subcutaneous dose in patients with atopic dermatitis (AD) were 108 μg/mL, 100 μg/mL, and 87 μg/mL, respectively. The $C_{max,ss}$, the $C_{avg,ss}$, and the $C_{trough,ss}$ following the 250 mg Q4W subcutaneous dose in patients with AD were 63 μg/mL, 51 μg/mL, and 36 μg/mL, respectively. The absolute bioavailability for a subcutaneous dose was estimated as 86%. EBGLYSS™ exhibited linear pharmacokinetics with dose-proportional increase in exposure over a dose range of 37.5 mg to 500 mg.

The total volume of distribution at steady-state was 5.14 L. Lebrikizumab is a mAb and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. In the population PK analysis, clearance was 0.154 L/day and was independent of dose. The mean elimination half-life was 24.5 days.

During the 12-month treatment period in EBGLYSS studies, 4/145 (2.8%) of subjects treated with 250 mg EBGLYSS every 2 weeks followed by 250 mg every four weeks developed antibodies to lebrikizumab, most of which were neutralizing and of low titer. No effect of immunogenicity on pharmacokinetics was observed due to the low occurrence of ADA.

A longitudinal exposure-response model describing the PK and EASI relationship predicted EASI 75 response rates of 80% for 250 mg Q4W, at Week 52 for subjects who initially received 250 mg Q2W and achieved EASI response criteria at Week 16.

2.3.2 Interaction Studies

As endogenous IgGs, the effect of lebrikizumab on the PK of co-administered medications and the effect of co-administered medications on lebrikizumab are not expected.

2.3.3 Special Populations

Based on population PK analysis, the pharmacokinetics of lebrikizumab were not affected by age, gender, or race except body weight. The $C_{avg,ss}$ was reduced by about 26% for the highest BW quartile (85.1 to 192 kg) and increased about 27% for the lowest BW quartile (39.6 to 58.5 kg). from the population PK analysis and the effect on PK did not result in clinically meaningful changes in EASI.

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the pharmacokinetics of lebrikizumab have not been conducted. Pop PK analysis showed that markers of renal (eGFR) and hepatic function (ALT and AST) did not affect the PK of lebrikizumab.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, three pivotal studies (KGAB, KGAC and KGAD) are provided to support the efficacy of EBGLYSSTM for the claimed indication. Of these three studies, Studies KGAB and KGAC were EBGLYSS monotherapy studies, and Study KGAD was a combination study of EBGLYSS with TCS (topical corticosteroids). The key efficacy results of these three studies are summarized below.

<u>EBGLYSS monotherapy studies (KGAB and KGAC)</u>

In the pooled KGAB and KGAC population, approximately half (49.9%) were female. The mean age was 35.8 year and 12% were adolescents. Most were White (63.7%) and one fifth of participants were Asian. Most of participants had moderate AD (61.5%) as determined by IGA, others had severe AD.

Both monotherapy studies met the FDA primary efficacy endpoint and the EMA co-primary efficacy endpoints (Table 2.4.1-1). In addition, in Study KGAB, there was a statistically significant improvement in all FDA and EMA major secondary endpoints at Week 16 with EBGLYSS 250 mg Q2W compared to placebo.

In contrast, in Study KGAC, EBGLYSS 250 mg Q2W demonstrated statistically significant improvements in all major secondary endpoints, except for the percentage of patients with a Pruritus NRS score of $\geqq$ 4 points at baseline who had a $\geqq$ 4-point reduction from baseline to Week 2 (Table 2.4.1-1).

Table 2.4.1-1 Results of FDA primary and EMA co-primary efficacy endpoints for both studies

	Study [KGAB]				Study [KGAC]			
	Placebo (N = 141)	EBGLYSS 250 mg Q2W (N = 283)	Treatment Effect (95% CI)	p-value	Placebo (N = 141)	EBGLYSS 250 mg Q2W (N = 283)	Treatment Effect (95% CI)	p-value
Primary or Co-Primary efficacy endpoints								
FDA Primary, EMA co-primary efficacy endpoints Percentage of patients with an IGA score of 0 or 1 and a reduction of ≧ 2 points from Baseline at Week 16	18 (12.7%)	122 (43.1%)	29.7% (21.6%, 37.8%)	< 0.001	16 (10.8%)	93 (33.2%)	21.9% (14.2%, 29.6%)	< 0.001
EMA co-primary efficacy endpoints, FDA Major Secondary endpoint Percentage of patients achieving EASI-75 (≧ 75% reduction from baseline in EASI) at Week 16	23 (16.2%)	166 (58.8%)	42.0% (33.3%, 50.6%)	< 0.001	26 (18.1%)	146 (52.1%)	33.3% (24.4%, 42.2%)	< 0.001
Major key secondary efficacy endpoints (FDA and EMA)								
Percentage of patients achieving EASI-90 (≧ 90% reduction from baseline in EASI) at Week 16	13 (9.0%)	108 (38.3%)	28.8% (21.3%, 36.3%)	< 0.001	14 (9.5%)	86 (30.7%)	20.7% (13.3%, 28.1%)	< 0.001
Percentage of patients with a Pruritus NRS of ≧ 4-points at baseline who achieve a ≧4-point reduction from baseline to Week 16	17 (13.0%)	121 (45.9%)	32.9% (24.6%, 41.3%)	< 0.001	15 (11.5%)	101 (39.8%)	28.3% (20.0%, 36.5%)	< 0.001
Percentage of patients with a Pruritus NRS of ≧ 4-points at baseline who achieve a ≧4-point reduction from baseline to Week 4	3 (2.3%)	56 (21.5%)	19.3% (13.7%, 25.0%)	< 0.001	4 (3.0%)	42 (16.8%)	13.2% (7.7%, 18.7%)	< 0.001
Percentage of patients with a Pruritus NRS of ≧ 4-points at baseline who achieve a ≧4-point reduction from baseline to Week 2	1 (0.9%)	16 (6.1%)	5.3% (1.9%, 8.6%)	0.017	1 (0.7%)	9 (3.6%)	2.7% (-0.1%, 5.4%)	0.113
Percentage of patients with a Sleep-loss ≧ 2 points at baseline who achieve a ≧ 2 points reduction from baseline at Week 16	4 (4.7%)	76 (39.0%)	34.6% (26.2%, 43.0%)	< 0.001	8 (8.2%)	45 (28.0%)	18.9% (9.6%, 28.1%)	< 0.001
Major key secondary efficacy endpoints (FDA only)								
Percentage of patients with an IGA score of 0 or 1 and a reduction ≧ 2 points at Week 16 in adults	14 (11.3%)	104 (42.2%)	30.8% (22.1%, 39.4%)	< 0.001	15 (11.5%)	80 (31.8%)	20.4% (12.3%, 28.6%)	< 0.001
Percentage of patients with an IGA score of 0 or 1 and a reduction ≧ 2 points at Week 4	1 (0.8%)	30 (10.6%)	9.6% (5.7%, 13.6%)	< 0.001	2 (1.4%)	25 (9.0%)	8.1% (4.1%, 12.0%)	0.002
Major key secondary efficacy endpoints (EMA only)								
Percentage change in EASI from baseline to Week 16, LSM (SE)	-26.0 (4.0)	-64.3 (3.2)	-38.3 (-46.4, -30.2)	< 0.001	-28.0 (3.9)	-61.5 (3.3)	-33.6 (-41.2, -26.0)	< 0.001
Percentage change in Pruritus NRS score from baseline to Week 16, LSM (SE)	-15.1 (3.8)	-45.5 (3.1)	-30.4 (-38.1, -22.7)	< 0.001	-9.02 (3.9)	-36.6 (3.3)	-27.5 (-34.9, -20.2)	< 0.001
Percentage of patients achieving EASI-90 at Week 4	2 (1.6%)	35 (12.4%)	10.7% (6.2%, 15.2%)	< 0.001	2 (1.5%)	18 (6.3%)	4.9% (1.4%, 8.4%)	0.023
Change from baseline in DLQI total score at Week 16, LSE (SE)	-2.9 (1.1)	-8.7 (1.1)	-5.8 (-7.1, -4.5)	< 0.001	-2.4 (1.2)	-7.3 (1.2)	-4.9 (-6.3, -3.5)	< 0.001
Change from baseline in Sleep-Loss score at Week 16, LSE (SE)	-0.4 (0.1)	-1.1 (0.1)	-0.79 (-1.0, -0.57)	< 0.001	-0.4 (0.1)	-1.1 (0.1)	-0.7 (-0.9, -0.5)	< 0.001
Percentage of patients with a DLQI total score of ≧ 4-points at baseline who achieve a ≧4-point reduction from baseline to Week 16	39 (33.8%)	171 (75.6%)	41.8% (31.2%, 52.3%)	< 0.001	39 (33.6%)	143 (66.3%)	33.0% (22.2%, 43.8%)	< 0.001

Combination study of EBGLYSS with TCS (KGAD)

In Study KGAD, about half (48.8%) were female. The mean age was 37.2 years and 21.8% were adolescents. Most were White (61.6%) and 14.7% of participants were Asian. The majority of participants had moderate AD (69.2%) as determined by IGA and severe AD corresponded to 30.8%. Study KGAD met the FDA primary efficacy endpoint and the EMA co-primary efficacy endpoints (Table 2.4.1-2). In addition, EBGLYSS 250 mg Q2W + TCS showed statistically significant improvements in all FDA and EMA major secondary endpoints at Week 16 compared to placebo (Table 2.4.1-2).

Table 2.4.1-2 Results of FDA primary endpoint and EMA co-primary efficacy endpoints for Study KGAD

	Placebo + TCM (N = 66)	EBGLYSS 250 mg Q2W + TCM (N = 145)	Treatment Effect (95% CI)	p-value
Primary or Co-primary endpoints				
FDA Primary, EMA Co-primary endpoint Percentage of patients with an IGA score of 0 or 1 and a reduction of ≧ 2 points from Baseline at Week 16	15 (22.1%)	60 (41.2%)	18.3% (5.1%, 31.5%)	0.011
EMA Co-primary endpoint, FDA Major Secondary Percentage of patients achieving EASI-75 (≧ 75% reduction from baseline in EASI) at Week 16	28 (42.2%)	101 (69.5%)	26.4% (12.1%, 40.8%)	< 0.001
Major secondary endpoints (FDA and EMA)				
Percentage of patients achieving EASI-90 (≧ 90% reduction from baseline in EASI) at Week 16	14 (21.7%)	60 (41.2%)	18.9% (6.1%, 31.7%)	0.008
Percentage of patients with a Pruritus NRS of ≧4-point at baseline who experience both EASI 75 and a≧4-point reduction in Pruritus NRS score from Baseline at Week 16	10 (16.8%)	50 (38.3%)	21.6% (8.3%, 35.0%)	0.005
Percentage of patients with a Pruritus NRS of ≧ 4-points at baseline who achieve a ≧4-point reduction from baseline to Week 16	18 (31.9%)	66 (50.6%)	19.2% (4.3%, 34.1%)	0.017
Major secondary endpoints (EMA only)				
Percent change in EASI from Baseline to Week 16, LSM (SE)	-53.1 (5.1)	-76.8 (4.1)	-23.6 (-33.6, 13.7)	< 0.001
Percent change in Pruritus NRS from Baseline to Week 16, LSM (SE)	-35.5 (6.4)	-50.7 (4.5)	-15.2 (-27.7, -2.7)	0.017
Change from Baseline in DLQI at Week 16, LSM (SE)	-6.5 (1.9)	-9.8 (1.8)	-3.3 (-5.3, -1.3)	0.036
Percentage of patients with a DLQI total score of ≧ 4-point at baseline who experience a ≧ 4-point improvement from Baseline to Week 16	28 (58.7%)	81 (77.4%)	17.2% (0.1%, 34.3%)	0.036
Change from Baseline in Sleep-loss score at Week 16, LSM (SE)	-0.8 (0.1)	-1.1 (0.1)	-0.3 (-0.6, 0.0)	0.025

Efficacy in adolescent subgroup were generally consistent with the results observed in the adult population across the 3 studies.

In summary, the results of the three pivotal studies (KGAB, KGAC and KGAD) provided sufficient evidence to support the efficacy of EBGLYSS 250 mg Q2W for the claimed indication.

2.4.2 Safety Results

The atopic dermatitis(AD) safety database included moderate-to-severe AD 1720 patients (372 adolescents) exposed to lebrikizumab at any dose. Among them, 891 patients (270 adolescents) were exposed to lebrikizumab for at least 1 year.

The overall frequencies of TEAEs, SAEs, and AEs leading to discontinuation from study drug were similar in the lebrikizumab and placebo groups and most events were mild or moderate in severity during the placebo-controlled Induction Period. The safety profile in the Maintenance Period revealed longer exposure to lebrikizumab did not result in an increased IR for TEAEs. The overall safety profile of lebrikizumab was comparable when used with or without TCS. Four deaths were reported in the lebrikizumab AD clinical program and no deaths were reported by the investigator as related to the study drug. ADRs of lebrikizumab treatment for AD are conjunctivitis, keratitis, ISRs, blood eosinophilia, and Herpes zoster. The safety profile in adolescents was consistent with the safety profile in adults.

2.5 Bridging Study Evaluation

Compared to non-East Asians, East Asians have similar Cmax and AUCtau in the first (week 0 to week 2), second (week 2 to week 4) and last (week 14 to week 16) dosing interval of the induction period. Additionally, no obvious ethnic factors were found after reviewing the issues in align with ICH E5 guidance. Therefore, none to minimally ethnically sensitive was determined from PK's perspective.

There were 94(11%) East Asians in the pooled KGAB and KGAC population. The efficacy of East Asian subgroup showed the same trend compared to the non-East Asian Subgroup in the Induction Period. The Japanese study KGAL (N=289) provided further information to support the use of LEB treatment in East Asian. The design of Study KGAL was similar to Study KGAB and KGAC except for combination with TSC. The efficacy and safety of Study KGAL were comparable with those observed in the global trials.

2.6 Conclusion

This multidisciplinary review recommends approval for EBGLYSS Injection (Lebrikizumab) indicated for the treatment of patients aged 12 years and older, weighing at least 40 kg, with moderate-to-severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not advisable. EBGLYSS can be used with or without topical corticosteroids

3. Post-Marketing Requirements

NA