swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ebglyss

International non-proprietary name:	lebrikizumab
Pharmaceutical form:	solution for injection in pre-filled syringe; solution for injection in pre-filled pen
Dosage strength(s):	250 mg / 2 mL
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	Almirall AG
Marketing authorisation no.:	69344; 69460
Decision and decision date:	approved on 30 August 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for lebrikizumab in the above-mentioned medicinal products.

2.2 Indication and dosage

2.2.1 Requested indication

Ebglyss is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years of age and older who are eligible for systemic therapy.

2.2.2 Approved indication

Ebglyss is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg when therapy with topical medicinal products does not provide adequate disease control or is not medically advisable.

2.2.3 Requested dosage

The recommended lebrikizumab dose for adult patients and adolescent patients aged 12 to 17 years with a body weight of at least 40 kg is 500 mg (2 × 250 mg injections) each at Week 0 and Week 2, followed by 250 mg administered subcutaneously every 2 weeks until Week 16.

The recommended maintenance dose of lebrikizumab is 250 mg every 4 weeks. In some patients, a sufficient clinical response can be maintained with a dose of 250 mg every 8 weeks.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	8 June 2023
Formal control completed	20 June 2023
List of Questions (LoQ)	19 October 2023
Response to LoQ	17 January 2024
Preliminary decision	11 April 2024
Response to preliminary decision	9 June 2024
Final decision	30 August 2024
Decision	approval

3 Medical context

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease. It is often associated with a personal or family history of atopy. A multiplicity of mechanisms is involved in the pathogenesis of AD, including epidermal barrier dysfunction, genetic factors, T helper type 2 (Th2) cell-skewed immune dysregulation, altered skin microbiome, and environmental triggers of inflammation.

AD affects between 5 and over 20 percent of children and approximately 10 percent of adults worldwide. In most cases, AD presents before the age of 5 years and persists beyond infancy in approximately 50 percent of patients. However, 1 in 4 adults with AD report adult onset of disease.

Dry skin and severe pruritus are the cardinal signs of AD. Acute AD presents with erythematous papules and vesicles with exudation and crusting, while subacute and chronic AD is characterised by dry, scaly, or excoriated papules or skin thickening (lichenification) from chronic scratching. However, the clinical presentation is highly variable, depending upon the patient's age, ethnicity, and disease activity. Atopic dermatitis follows a chronic, relapsing course over months to years. The diagnosis of atopic dermatitis is clinical, based upon history, morphology, and distribution of skin lesions, and associated clinical signs.

The goals of treatment of atopic dermatitis are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimise therapeutic risks. Management involves elimination of exacerbating factors, restoration of the skin barrier function and hydration of the skin, patient education, and pharmacologic treatment of skin inflammation.
Patients with mild to moderate symptoms are generally managed with topical therapies. For patients with moderate to severe disease who have an inadequate response to topical therapies, biologics or JAK inhibitors are recommended.

4 Quality aspects

4.1 Drug substance

Lebrikizumab is a monoclonal antibody based on a human immunoglobulin G4 (IgG4) framework, which is directed against interleukin (IL)-13. Lebrikizumab is a glycoprotein (molecular weight approx. 145 KDa) composed of 2 heavy chains of 445 amino acids and 2 light chains of 218 amino acids, which are linked through inter-chain disulfide bonds.

Lebrikizumab is produced in Chinese Hamster Ovary (CHO) cells. A two-tiered cell banking system of Master Cell Bank and Working Cell Bank (WCB) is in place. After thawing of the WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The cell culture fluid is harvested, and purification is performed with a series of chromatography, ultra-/diafiltration, viral inactivation, and viral filtration steps.

The fermentation and purification processes for lebrikizumab drug substance are both validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.

Several changes were implemented during development of the manufacturing process for lebrikizumab drug substance, including changes to manufacturing site and production scale. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of lebrikizumab and its impurities were performed using state-of-the-art methods.

The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on clinical experience, batch analysis data, and stability data, and conform to current compendial or regulatory guidelines.

Batch analysis data for development, clinical, and process validation batches of the drug substance were provided. All specific analytical methods are described and are fully validated.

The drug substance is stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

4.2 Drug product

Lebrikizumab injection, 250 mg/2 mL, is supplied as a sterile, non-pyrogenic parenteral solution for subcutaneous administration. The finished product is contained in a 2.25 mL glass syringe barrel with laminated elastomeric plunger.

Lebrikizumab drug substance is an aqueous frozen solution comprising the active pharmaceutical ingredient lebrikizumab (nominally 125 mg/mL), including the excipients histidine acetate, sucrose, and polysorbate 20 of compendial grade, which are commonly used in the formulation of biopharmaceuticals. For lebrikizumab drug product, the active pharmaceutical ingredient and excipient concentrations in the drug substance and drug product are the same.

Several drug product dosage strengths, formulations, presentations, and filling facilities were used during clinical development. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability of the relevant quality attributes between the different processes.

The materials of the Type I glass syringe barrel and laminated elastomeric plunger meet compendial requirements.
Compatibility studies were conducted to establish the in-use stability of the drug product with the intended materials and conditions of use.

The drug product manufacturing process consists of thawing of the formulated drug substance, dilution and mixing, bioburden-reducing filtration, sterile filtration and aseptic filling, crimping, visual inspection, labelling, and secondary packaging.

The drug product manufacturing process is validated with several consecutive batches. The data demonstrated consistent production.

The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data were provided for several batches of the drug product, including development batches, clinical batches, and process validation batches. All batch release data comply with the drug product specifications valid at the time of testing. All specific analytical methods are validated.

The drug product (pre-filled syringe with needle safety device) should be stored at 2°C to 8°C protected from light. The stability data support a shelf life of 36 months.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated. Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

5 Nonclinical aspects

The nonclinical development programme for Ebglyss, containing the new active substance lebrikizumab, followed relevant ICH guidelines. The pivotal safety studies were performed in compliance with GLP regulations.

5.1 Pharmacology

The pharmacodynamic *in vitro* and *in vivo* studies demonstrated that lebrikizumab specifically blocks the action of IL-13 and identified the cynomolgus monkey as the relevant nonclinical species.

The affinity (K_D) of lebrikizumab to the IL-4Rα interface of IL-13 in humans and cynomolgus monkeys was determined to be 31 pM and < 0.67 pM, respectively. Lebrikizumab did not bind to rat or mouse IL-13, which therefore are not relevant nonclinical species. *In vitro,* lebrikizumab inhibited IL-13-induced phosphorylation of signal transducer and activator of transcription 6 (STAT6) in TF-1 cells as well as IL-13-induced proliferation of TF-1 cells and Hodgkin lymphoma cell lines. *In vivo,* lebrikizumab demonstrated efficacy in human IL-13-mediated acute lung inflammation in mice. Following administration, decreased inflammation was observed, characterised by a reduction in inflammatory cells and TGFβ1 levels. Since proof of concept was demonstrated in the nonclinical pharmacology studies and efficacy for the applied indication (atopic dermatitis, AD) has been evaluated in clinical studies, the lack of studies in an animal model for AD can be accepted.

Due to its low potential for binding to Fc receptors, the risk of induction of relevant effector functions by lebrikizumab (IgG4) is considered low.

Safety pharmacology endpoints in the cardiovascular, central nervous, and respiratory systems were incorporated into the toxicology studies conducted in cynomolgus monkeys. No lebrikizumab-related effects were observed.

5.2 Pharmacokinetics

The pharmacokinetic profile of lebrikizumab in cynomolgus monkeys following subcutaneous administration revealed dose-exposure proportionality, a long half-life of up to 25 days, and a volume of distribution similar to total plasma volume, suggesting that lebrikizumab mainly distributes in circulating blood. There were no sex- or age-related differences. The pharmacokinetic parameters are comparable with those in humans.

In cynomolgus monkeys, lebrikizumab was measured in fetuses and offspring, showing that lebrikizumab crosses the placenta.

In accordance with ICH S6(R1), studies on metabolism or excretion were not conducted.

Lebrikizumab led to the formation of anti-drug antibodies (ADA) in monkeys. Treatment-emergent antibody formation in the nonclinical studies did not affect lebrikizumab serum concentrations or its toxicity profile.

5.3 Toxicology

The toxicological profile of lebrikizumab was well characterised in repeat-dose toxicology studies in cynomolgus monkeys up to 9 months and at doses up to 25 mg/kg administered subcutaneously (SC) once weekly. The treatment was well tolerated and there were no lebrikizumab-related antemortem or post-mortem findings.

In accordance with ICH S6(R1), no genotoxicity studies were conducted.

According to ICH S6(R1), carcinogenicity studies are not warranted and were not conducted. Lebrikizumab does not bind murine IL-13 and rodent species are therefore not considered relevant for assessment of carcinogenic risk. No neoplastic lesions or histopathological evidence of preneoplastic changes were observed in any organs or tissues of monkeys following chronic administration of

lebrikizumab at exposure 24-fold higher than the clinical exposure. The applicant provided a comprehensive carcinogenicity assessment showing that an increased cancer risk is not expected in the intended patient population. Therefore, the carcinogenicity potential is considered low. However, the long-term safety of lebrikizumab, for events with low frequency and/or long latency including malignancies, is considered as missing information in the RMP and will be further assessed in the post-marketing setting.

Studies to evaluate the reproductive and developmental safety profile of lebrikizumab included separate fertility studies in sexually mature male and female cynomolgus monkeys, an embryo-fetal development (EFD) study, and an enhanced pre- and postnatal developmental (ePPND) study with 6-month observation of the infants. Lebrikizumab was well tolerated in both sexes when administered up to 25 mg/kg SC in males or intravenously in females, with no effects on male and female fertility endpoints. Systemic exposures at the NOAEL (25 mg/kg) were 13- and 20-fold above clinical exposure, respectively, based on C_{max}. In the early embryonic development study, lebrikizumab was not maternotoxic, embryotoxic, or teratogenic. In the pre/postnatal development study, lebrikizumab was well tolerated by maternal monkeys, with no test item-related effects. No lebrikizumab-related changes in any of the parameters measured, which included an immunotoxicology assessment, were noted in offspring from birth to 6 months postpartum. Lebrikizumab concentrations were quantifiable in serum samples from fetuses and offspring, showing that lebrikizumab crosses the placenta. Although there were no adverse findings in these studies, the use of lebrikizumab during pregnancy and lactation is not recommended due to transfer via the placenta and/or in milk. This is adequately reflected in the Information for healthcare professionals.

No specific studies in juvenile animals have been conducted with lebrikizumab given the preclinical development programme including juvenile, peri-pubertal adolescent, and sexually mature animals. Nonclinical studies were not foreseen in the PIP agreed by the EMA/PDCO for the paediatric population from 6 to less than 18 years of age.

Local tolerance following SC administration assessed in the toxicity studies in monkeys showed low irritation potential of lebrikizumab.

When considering the clinical C_{max} value of 108 µg/mL, the systemic exposures based on C_{max} at the NOAELs in the toxicity studies with lebrikizumab are multiple times higher than the predicted human therapeutic exposures in patients with AD.

The risk of immunotoxicity is low given that no treatment-related adverse effects on the innate and humoral immune systems were identified in any study in adult and infant monkeys. Exposure to lebrikizumab in cynomolgus monkeys up to 6 months of age was not associated with immunosuppression. However, an infection risk in humans cannot be predicted from the animal model and will be monitored as part of routine pharmacovigilance activities.

There are no safety concerns regarding excipients, drug substance- or drug product-related impurities/degradation products, and identified extractables/leachables from the container closure system.

Based on the ERA, there is no particular risk for the environment.

5.4 Nonclinical conclusions

In conclusion, the nonclinical documentation is sufficient to support the approval of Ebglyss (lebrikizumab) in the proposed indication. The pharmacodynamic studies and the safety programme do not suggest any particular adverse effects in patients. All nonclinical data relevant to safety are mentioned in the Information for healthcare professionals. From a nonclinical perspective, approval may be granted in the proposed indication.

6 Clinical aspects

6.1 Clinical pharmacology

Absorption
Following a 250 mg subcutaneous dose of lebrikizumab, peak serum concentrations were reached approximately 7-8 days after dosing. The absolute bioavailability was 86%. The injection site had no relevant influence on the absorption of lebrikizumab.
Following the 500 mg loading doses in Week 0 and Week 2, steady-state serum concentrations were reached with the first 250 mg Q2W dose in Week 4.

Distribution
Based on a population pharmacokinetic analysis, the volume of distribution at steady state was 5.14 L.

Elimination
The metabolism of lebrikizumab has not been characterised. As a human mAb, lebrikizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same way as endogenous IgG.
Based on a population pharmacokinetic analysis, the clearance was 0.154 L/day and the mean half-life was 24.5 days.

Dose linearity
Lebrikizumab showed linear pharmacokinetics with a dose-proportional increase in exposure over a dose range of 37.5 to 500 mg when administered as a subcutaneous injection.

Special populations / Intrinsic factors
No specific clinical pharmacology studies to evaluate the effect of renal or hepatic impairment on the PK of lebrikizumab have been conducted. This is acceptable based on the mechanism of action and biological nature of the molecule. Potential effects of covariates such as age, sex, and ethnicity were investigated in a population pharmacokinetic analysis, which indicated no significant effect on the pharmacokinetics of lebrikizumab.
Based on a population pharmacokinetic analysis, adolescents 12 to 17 years of age with atopic dermatitis had slightly higher lebrikizumab serum trough concentrations compared to adults, which was related to their lower body weight distribution.

Interactions
No dedicated pharmacokinetic drug-drug interaction studies have been conducted. The risk of lebrikizumab causing cytokine-mediated interactions with CYP enzymes in patients with atopic dermatitis is considered low.

Mechanism of action
Lebrikizumab is an immunoglobulin (IgG4) monoclonal antibody that binds with high affinity to interleukin (IL)-13 and selectively inhibits IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/ IL-13 receptor alpha 1 (IL-13Rα1) heterodimer, thereby inhibiting the downstream effects of IL-13.

6.2 Dose finding and dose recommendation

In the Phase 2b dose-ranging study J2T-DM-KGAF, the efficacy of 3 lebrikizumab doses compared to placebo was evaluated over 16 weeks in patients with moderate to severe AD. Patients were randomised to one of the following dosing regimens:

- Baseline loading dose of lebrikizumab 250 mg, followed by lebrikizumab 125 mg Q4W (every 4 weeks)
- Baseline loading dose of lebrikizumab 500 mg, followed by lebrikizumab 250 mg Q4W

- Baseline and Week 2 loading doses of lebrikizumab 500 mg, followed by lebrikizumab 250 mg Q2W (every 2 weeks)
- Placebo Q2W

The primary efficacy endpoint was the percent change in EASI (eczema area and severity index) from baseline to Week 16. All 3 lebrikizumab dosing groups met the primary efficacy endpoint with statistically significant greater reductions in EASI compared to placebo. In addition, the secondary endpoints showed statistically significant better responses to lebrikizumab compared to placebo but only for the 250 mg Q2W and 250 mg Q4W doses. However, the highest efficacy was observed with the lebrikizumab 250 mg Q2W dose. No significant safety differences were observed between the 3 lebrikizumab dosing groups. Therefore, the chosen lebrikizumab induction dose of 250 mg Q2W for the Phase 3 studies can be accepted.

6.3 Efficacy

The 3 pivotal studies were J2T-DM-KGAB, J2T-DM-KGAC, and J2T-DM-KGAD.

The 2 monotherapy studies J2T-DM-KGAB and J2T-DM-KGAC were identical in design. They consisted of an initial 16-week induction period where response to lebrikizumab 250 mg Q2W (after a loading dose of 500 mg lebrikizumab at baseline and Week 2) compared to placebo was evaluated, and a subsequent 36-week maintenance period where the durability of the efficacy compared to placebo (lebrikizumab withdrawal) was evaluated in participants given lebrikizumab 250 mg either Q4W or Q2W. Both studies included patients with moderate to severe AD. The co-primary endpoints were the percentage of participants with an IGA score (investigator's global assessment) of 0 or 1 and a ≥2-point reduction from baseline to Week 16 and the percentage of participants achieving EASI 75 (≥75% reduction from baseline in EASI) at Week 16. For multiplicity controlled major secondary endpoints, see the Information for healthcare professionals.

All of the primary and major secondary endpoints of the induction period were met in study KGAB. In the maintenance period, around 75-80% of lebrikizumab responders maintained improvements in skin clearance, disease severity, and pruritus (although differences between the lebrikizumab arms and the placebo arm were not statistically significant).

The primary endpoints of the induction period were met in study KGAC. Most of the major secondary endpoints were also met, except for the percentage of participants with a 4-point reduction of NRS at Week 2, indicating a slight delay in itch reduction.
In the maintenance period, around 80-85% of lebrikizumab responders maintained improvements in skin clearance, disease severity, and pruritus (although differences between the lebrikizumab arms and the placebo arm were not statistically significant).

The benefit of lebrikizumab monotherapy in the induction period compared to placebo could therefore clearly be demonstrated. However, the results for lebrikizumab in the maintenance phase were not statistically significant better compared to the placebo (withdrawal) arm in both pivotal studies. In its response to the LoQ, the Applicant demonstrated, that when pooling the maintenance phase of both pivotal studies, the results in the lebrikizumab group were statistically significantly superior to the placebo group during the maintenance period. The results are also considered clinically relevant. Therefore, the benefit of lebrikizumab monotherapy could also be demonstrated for the maintenance period.
Notably, maintenance dosing with lebrikizumab Q4W provided similar clinical responses to lebrikizumab Q2W. Therefore, the selection of the Q4W dose for maintenance therapy can be accepted.

The combination of lebrikizumab with topical corticosteroids (TCS) was evaluated in study J2T-DM-KGAD. This study consisted of a 16-week period where lebrikizumab 250 mg Q2W + topical corticosteroids were evaluated compared to placebo Q2W + topical corticosteroids. The co-primary

endpoints were the percentage of participants with an IGA score of 0 or 1 and a ≥2-point reduction from baseline to Week 16 and the percentage of participants achieving EASI 75 at week 16. For multiplicity controlled major secondary endpoints, see the Information for healthcare professionals.

The co-primary and major secondary endpoints were met, demonstrating statistically significant efficacy results for lebrikizumab + TCS compared to placebo + TCS. Therefore, the benefit of lebrikizumab with concomitant TCS was demonstrated.

Study J2T-DM-KGAA is an ongoing, 100-week study that was designed to describe the long-term safety and efficacy of lebrikizumab. However, as it has only yielded efficacy data from a subgroup of patients, no firm conclusions regarding long-term efficacy can be drawn yet.

Study J2T-DM-KGAE was an open-label, single arm study to evaluate the safety and efficacy of lebrikizumab in adolescent patients with moderate to severe AD. At Week 52, 62.6% of the participants achieved IGA 0 or 1 and 81.9% of participants achieved EASI 75. However, due to the open-label design of this study and the different dosing regimen (lebrikizumab 250 mg Q2W until Week 52), this study can only be considered as supportive.

A total of 354 adolescents (≥ 12 years of age and weighing 40 kg or more) were included across all lebrikizumab clinical studies. Comparing the results of the adolescent population in the induction period to the overall population, the responder rates in adolescents were even higher, demonstrating a clear benefit for lebrikizumab in adolescents up to 16 weeks. However, no direct formal comparison to the adult population only was made. Furthermore, blinded data over 52 weeks from studies KGAB and KGAC are sparse, with only 8 adolescents in the placebo, 17 in the lebrikizumab 250 mg Q4W, and 13 in the lebrikizumab 250 mg Q2W arms. Although study KGAE provided additional data regarding efficacy in adolescents up to 52 weeks, this was in an open-label setting and also used another dosing regimen (Q2W), therefore limiting firm conclusions in this age group. Overall, although the longer-term data in adolescents are still sparse, in its response to the LoQ, the Applicant provided side-by-side comparisons of efficacy results in adolescents and adults. In the induction and also the maintenance periods, the results were mostly similar or even better in adolescents compared to the adult population. In addition, the safety data were similar to the adult population. Therefore, the benefit-risk assessment is also considered positive for this age group.

6.4 Safety

A total of 1720 participants (including 372 adolescents) were exposed to any dose of lebrikizumab for 1637.02 PY. Overall, 891 participants (270 adolescents) were exposed to any dose of lebrikizumab for at least 1 year and 59 patients for more than 104 weeks. In addition, 147 participants received the proposed Q2W induction and Q4W maintenance therapy.

The integrated safety analysis was based on the different sets. The most important sets were AD ALL PC Weeks 0 to 16 (AD induction period placebo-controlled set including studies KGAF, KGAB, KGAC, and KGAD), AD Mono PC Weeks 16 to 52 (AD maintenance period placebo-controlled set including studies KGAB and KGAC), AD Mono/TCS Weeks 0 to 52/56 (AD combined induction and maintenance periods set including studies KGAB, KGAC, KGAD, KGAA), and AD All LEB (AD all lebrikizumab exposure set).

Overall, a higher percentage of patients in the placebo group had treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) compared to the lebrikizumab group in the AD ALL PC set during the induction period. Only discontinuations of the study drug due to AEs occurred at a higher percentage in the lebrikizumab group compared to the placebo group. In the combined induction and maintenance set a slightly higher percentage in the lebrikizumab groups had TEAEs and SAEs compared to the placebo (lebrikizumab withdrawal) group.

The most common AEs that were reported more frequently (>0.3% difference) in the lebrikizumab group compared to placebo in the AD ALL PC Weeks 0-16 set were conjunctivitis, nasopharyngitis, headache, conjunctivitis allergic, dry eye, rhinitis allergic, herpes zoster, thrombocytopenia, and injection site rash.

Serious adverse events occurred in a higher percentage of patients receiving placebo (1.9%) compared to patients receiving lebrikizumab (1.3%) in the AD ALL PC Weeks 0-16 set. No SAE occurred in more than 1 patient and no clusters could be observed. In the AD All LEB set, 56 patients (3.3%) had at least 1 SAE. Except for AD (n=3), COVID-19 (n=2), and multiple injuries (n=2), no SAE was reported in more than 1 patient.

Four deaths were reported in the lebrikizumab AD clinical programme. Three deaths (pancreatic cancer, natural cause, cardiac arrest) were reported in participants treated with lebrikizumab 250 mg Q2W. The evaluation of causality of these deaths remains difficult, as no autopsy was performed for ‘natural cause’ and ‘cardiac arrest’ and no certain reason for death can be identified. However, there are no indications that these deaths would somehow be related to lebrikizumab. One death due to myocardial infarction was reported in the placebo group during the 16-week induction period of study KGAC.

Regarding safety topics of special interest, the AEs of conjunctivitis and keratitis occurred in a higher percentage of patients in the lebrikizumab group compared to placebo and are already known from other monoclonal antibodies that target the IL-13 pathway. Regarding other safety topics of special interest (infections, eosinophil-related disorder, injection site reactions, hepatic-related TEAEs, and malignancies), no major imbalances or concerns were observed.

Of the total of 1187 participants in the AD ALL PC set, 147 were adolescents. In this AD ALL PC set, the safety data in adolescents were slightly better compared to the adult population. In addition, safety data in a total of 372 adolescents were collected in the AD All LEB safety set. In this set, the overall safety profile in adolescents was similar to that of the adult patients.

Although long-term data are still sparse, overall, lebrikizumab demonstrated a favourable safety profile, with the most common side effects being conjunctivitis, injection site reactions, allergic conjunctivitis, and dry eye, and no prohibitive safety concerns could be identified.

6.5 Final clinical benefit-risk assessment

AD is a chronic, pruritic, inflammatory skin disease and affects between 5 and over 20 percent of children and approximately 10 percent of adults worldwide. Dry skin and severe pruritus are the cardinal signs of AD. The goals of treatment of atopic dermatitis are to reduce symptoms, prevent exacerbations, and minimise therapeutic risks. Patients with mild to moderate symptoms are generally managed with topical therapies. For patients with moderate to severe disease who have an inadequate response to topical therapies, biologics or JAK inhibitors are recommended.

The clinical pharmacology characteristics of lebrikizumab were sufficiently characterised in healthy subjects and the intended patient population.

The two monotherapy studies J2T-DM-KGAB and J2T-DM-KGAC were identical in design and consisted of an initial 16-week induction period where response to lebrikizumab 250 mg Q2W compared to placebo was evaluated, and a subsequent 36-week maintenance period where the durability of the efficacy compared to placebo was evaluated in patients with moderate to severe AD. In both studies, the primary endpoints and most of the secondary endpoints were met, demonstrating a statistically and clinically relevant benefit over placebo.

Study J2T-DM-KGAD evaluated the combination of lebrikizumab with TCS**.** The primary and major secondary endpoints were also met in this study, demonstrating statistically significant efficacy results for lebrikizumab + TCS compared to placebo + TCS.
A relevant proportion of patients included in the 3 studies were adolescents. Efficacy was generally similar or even better compared to the adult population.

Although long-term data are still sparse, overall, lebrikizumab demonstrated a favourable safety profile. The most common adverse events were conjunctivitis, injection site reactions, allergic conjunctivitis, and dry eye. Only a small number of SAEs occurred and most of them were single cases.

Due to the described benefits and the favourable safety profile, the overall benefit-risk assessment of lebrikizumab is considered positive for adults and adolescents (≥ 12 years of age and weighing 40 kg or more) in the induction period and the maintenance period as monotherapy and also with concomitant TCS.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Ebglyss, solution for injection in pre-filled syringe, and Ebglyss, solution for injection in pre-filled pen, was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Ebglyss®

Composition

Active substances

Lebrikizumab.
Lebrikizumab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipients

Histidine, acetic acid 99%, sucrose, polysorbate 20, water for injection

Pharmaceutical form and active substance quantity per unit

Solution for subcutaneous injection.

Ebglyss, solution for injection in pre-filled syringe

Each single-use pre-filled syringe contains 250 mg of lebrikizumab in 2 ml solution (125 mg/ml).

Ebglyss, solution for injection in pre-filled pen

Each single-use pre-filled pen contains 250 mg of lebrikizumab in 2 ml solution (125 mg/ml).

Clear to opalescent, colourless to slightly yellow to slightly brown solution, free of visible particles.

Indications/Uses

Ebglyss is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg when therapy with topical medicinal product does not provide adequate disease control or is not medically advisable.

Dosage/Administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis.

Usual dosage

The recommended dose of lebrikizumab is 500 mg (two 250 mg injections) at both week 0 and week 2, followed by 250 mg administered subcutaneously every other week up to week 16.
Consideration should be given to discontinuing treatment in patients who have shown no clinical response after 16 weeks of treatment.
Once clinical response is achieved, the recommended maintenance dose of lebrikizumab is 250 mg every fourth week.
Lebrikizumab can be used with or without topical corticosteroids (TCS). Topical calcineurin inhibitors (TCI) may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special dosage instructions

Patients with impaired hepatic or renal function

No dose adjustment is required for patients with hepatic or renal impairment (see «Pharmacokinetics»).

Body weight

No dose adjustment for body weight is required (see «Pharmacokinetics»).

Elderly patients (≥65 years of age)

No dose adjustment is required for elderly patients (see «Pharmacokinetics»).

Children less than 12 years of age

The safety and efficacy of lebrikizumab in children aged less than 12 years or adolescents 12 to 17 years of age and weighing less than 40 kg has not yet been established. No data are available.

Mode of administration

Subcutaneous use.

Lebrikizumab is administered by subcutaneous injection into the thigh or abdomen, except for 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.
For the initial 500 mg dose, two 250 mg injections should be administered consecutively in different injection sites.
It is recommended to rotate the injection site with each injection. Lebrikizumab should not be injected into skin that is tender, damaged or has bruises or scars.
A patient may self-inject lebrikizumab or the patient's caregiver may administer lebrikizumab if their physician determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the administration of lebrikizumab prior to use. Detailed instructions for use are included at the end of the package leaflet.

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see «Composition»).

Warnings and precautions

Hypersensitivity

If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of lebrikizumab should be discontinued and appropriate therapy initiated.

Conjunctivitis

Patients treated with lebrikizumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination (see «Undesirable efffects»).
Patients must report any new or worsening eye symptoms to their physician.

Vaccinations

Prior to initiating therapy with lebrikizumab, consider completion of all age-appropriate immunisations according to current immunisation guidelines. Live and live attenuated vaccines should not be given concurrently with lebrikizumab as clinical safety and efficacy has not been established. Immune responses to non-live vaccines were assessed in a combined tetanus, diphtheria and acellular pertussis vaccine (TdaP) and a meningococcal polysaccharide vaccine (see «Interactions»).

Helminthosis

Patients with known helminthosis were excluded from the clinical trials. Patients with pre-existing helminthosis should be treated before initiating treatment with lebrikizumab. If the patient becomes infected during treatment with lebrikizumab and does not respond to treatment for helminthosis, treatment with lebrikizumab must be suspended until the infection has resolved.

Interactions

Live vaccines

The safety and efficacy of concurrent use of lebrikizumab with live and live attenuated vaccines has not been studied. Live and live attenuated vaccines should not be given concurrently with lebrikizumab (see also «Warnings and precautions»).

Non-live vaccines

Immune responses to non-live vaccines were assessed in a study in which adult patients with atopic dermatitis were treated with lebrikizumab 500 mg at weeks 0 and 2 followed by lebrikizumab 250 mg every other week until week 16. After 12 weeks of lebrikizumab administration, patients were vaccinated with a combined tetanus, diphtheria, and acellular pertussis vaccine TdaP vaccine (T cell-dependent) and a meningococcal polysaccharide vaccine (T cell-independent). Immune responses to tetanus toxoid and polysaccharide vaccine against serogroup C meningococcus were assessed 4 weeks later. Antibody responses to both non-live vaccines were not negatively impacted by the concomitant lebrikizumab treatment. No adverse interactions between the non-live vaccines and lebrikizumab were noted in the study.

Concomitant therapies

No studies to record pharmacokinetic drug interactions have been performed.
The risk of lebrikizumab causing cytokine-mediated interactions with CYP enzymes in patients with atopic dermatitis is estimated to be low.

Pregnancy, lactation

Pregnancy

There are limited amount of data from the use of Ebglyss in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see «Preclinical data»). Lebrikizumab should not be used during pregnancy unless the potential benefit exceeds the potential risk to the fetus.

Lactation

It is unknown whether lebrikizumab is excreted in human milk or absorbed systemically after ingestion. Maternal IgG is known to be present in human milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or the Ebglyss therapy. Both the benefit of breast feeding for the child and the benefit of therapy for the mother must be weighed.

Fertility

The effect of Ebglyss on fertility in humans has not been studied. Animal studies showed no impairment of fertility (see «Preclinical data»).

Effects on ability to drive and use machines

No corresponding studies have been conducted.

Undesirable effects

Summary of the safety profile

The most common adverse reactions are conjunctivitis (6.9%), injection site reactions (2.6%), conjunctivitis allergic (1.8%) and dry eye (1.4%).

Tabulated list of adverse reactions

Across all clinical studies in atopic dermatitis, a total of 1720 patients were administered lebrikizumab, of which 891 patients were exposed to lebrikizumab for at least one year. Unless otherwise stated, the frequencies are based on a pool of 4 randomised, double-blind studies in patients with moderate-to-severe atopic dermatitis where 783 patients were treated with subcutaneous lebrikizumab during the placebo-controlled period (first 16 weeks of treatment).
Listed in Table 1 are adverse reactions observed from clinical trials presented by system organ class and frequency, using the following categories: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1 000, <1/100); rare (≥1/10 000, <1/1 000); very rare (<1/10 000).

Table 1. List of adverse reactions

MedDRA System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Common Uncommon	Conjunctivitis Herpes zoster
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Eye disorders	Common Uncommon	Conjunctivitis allergic Dry eye Keratitis Blepharitis
General disorders and administration site conditions	Common	Injection site reaction

Description of specific adverse reactions and additional information

Conjunctivitis and related events

During the first 16 weeks of treatment conjunctivitis, conjunctivitis allergic, blepharitis and keratitis were reported more frequently in patients treated with lebrikizumab (6.9%, 1.8%, 0.8% and 0.6% respectively) compared to placebo (1.8%, 0.7%, 0.2% and 0.3%). Most cases of conjunctivitis, conjunctivitis allergic, blepharitis and keratitis were mild or moderate in severity, recovered or resolved without treatment interruption, or discontinuation.

Eosinophilia

Lebrikizumab-treated patients had a greater mean increase from baseline in eosinophil count compared to patients treated with placebo. In general, the increase from baseline in the lebrikizumab-treated patients was only transient.
Eosinophilia (>5000 cells/µL) was observed in 0.4% lebrikizumab-treated patients and none of the placebo-treated patients. Eosinophilia did not result in treatment discontinuation and no eosinophil-related disorders were reported.
Infections
Across all clinical studies in atopic dermatitis severe infections during the initial 16 weeks were observed in 0.4% lebrikizumab-treated patients and 0.5% of patients treated with placebo.

Injection site reactions

Injection site reactions (including pain, erythema and rash) were reported more frequently in patients who received lebrikizumab (2.6%) compared to placebo (1.5%). The majority (95%) of injection site reactions were mild or moderate in severity, and few patients (<0.5%) discontinued lebrikizumab treatment.

Herpes zoster

Herpes zoster was reported in 0.6% of the patients treated with lebrikizumab and none of the patients in the placebo group. All herpes zoster events reported were mild or moderate in severity and none led to permanent discontinuation of treatment.

Immunogenicity

As with all therapeutic proteins, there is a possibility of immunogenicity with lebrikizumab. The incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the test. In addition, the observed incidence of antibody positivity (including neutralising antibodies) in a test can be influenced by several factors, such as test methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For this reason, comparing the incidence of antibodies to lebrikizumab with the incidence of antibodies to other drugs may be misleading.

With 12 months of treatment, up to 2.8% of patients treated with 250 mg lebrikizumab developed anti-drug antibodies (ADAs), most of which were neutralising and of low titer.

Long term safety

The long-term safety of lebrikizumab was assessed in 5 clinical studies. In the two monotherapy studies (ADvocate-1, ADvocate-2) up to 52 weeks and in patients enrolled in the TCS combination therapy study (ADhere) and followed in a long-term extension study (ADjoin) for a total of 56 weeks and the monotherapy ADore study in adolescents for also up to 52 weeks. The safety profile of lebrikizumab as monotherapy through week 52 or in combination with TCS through week 56 is consistent with the safety profile observed up to week 16.

Paediatric population

Adolescents 12 to 17 years of age

The safety of lebrikizumab was assessed in 372 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis, including 270 patients exposed for at least one year. The safety profile of lebrikizumab in these patients was similar to the safety profile in adults with atopic dermatitis.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Single intravenous doses up to 10 mg/kg and multiple subcutaneous doses up to 500 mg have been administered to humans in clinical trials without dose-limiting toxicity. There is no specific treatment for lebrikizumab overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

Properties/Effects

ATC code

D11AH10

Mechanism of action

Lebrikizumab is an immunoglobulin (IgG4) monoclonal antibody that binds with high affinity to interleukin (IL)13 and selectively inhibits IL13 signalling through the IL4 receptor alpha (IL4Rα)/IL-13 receptor alpha 1 (IL13Rα1) heterodimer, thereby inhibiting the downstream effects of IL13. Inhibition of IL13 signalling is expected to be of benefit in diseases in which IL13 is a key contributor to the

disease pathogenesis. Lebrikizumab does not prevent the binding of IL13 to the IL13 receptor alpha 2 (IL13Rα2 or decoy receptor), which allows the internalisation of IL13 into the cell.

Pharmacodynamics

In lebrikizumab clinical studies, lebrikizumab reduced the levels of serum periostin, total immunoglobulin E (IgE), CC chemokine ligand (CCL)17 [thymus and activation-regulated chemokine (TARC)], CCL18 [pulmonary and activation-regulated chemokine (PARC)], and CCL13 [monocyte chemotactic protein-4 (MCP-4)]. The decreases in the type 2 inflammation mediators provide indirect evidence of inhibition of the IL-13 pathway by lebrikizumab.

Clinical efficacy

Adults and adolescents with atopic dermatitis

The efficacy and safety of lebrikizumab as monotherapy (ADvocate-1, ADvocate-2) and with concomitant TCS (ADhere) were evaluated in three randomised, double-blind, placebo-controlled pivotal studies in 1062 adults and adolescents (aged 12 to 17 years and weighing ≥40 kg) with moderate-to-severe atopic dermatitis, defined by an Eczema Area and Severity Index (EASI) ≥16, Investigator's Global Assessment (IGA) ≥3, and a body surface area (BSA) involvement of ≥10%. Patients enrolled into the three studies previously had an inadequate response to topical medication or determination that topical treatments are otherwise medically inadvisable (the latter criterion did not apply for the ADhere study).
In all three studies, patients received an initial dose of 500 mg of lebrikizumab (two 250 mg injections) at weeks 0 and 2, followed by 250 mg every other week (Q2W) until week 16, or matching placebo in a 2:1 ratio. In ADhere, study patients also received concomitant low-to-mid potency TCS or TCI on active lesions. Patients were permitted to receive rescue treatment at the discretion of the investigator to control intolerable symptoms of atopic dermatitis. Patients requiring systemic rescue treatment were discontinued from study treatment.
Patients achieving IGA 0 or 1 or at least a 75% reduction in EASI (EASI 75) without having received any rescue therapy were re-randomised in a blinded manner to (i) lebrikizumab 250 mg every two weeks (Q2W); (ii) lebrikizumab 250 mg every 4 weeks (Q4W); or (iii) matching placebo up to 52 weeks.
In ADvocate-1 and ADvocate-2, after completing the 52-week study, and in ADhere, after completing the 16-week study, patients were offered the option to continue treatment in a separate long-term extension study (ADjoin).

Endpoints

In all three studies, the co-primary endpoints were the percentage of patients with IGA 0 or 1 ("clear" or "almost clear"), with a ≥2-point reduction from baseline, and the percentage of patients achieving 75% reduction in EASI (EASI 75) from baseline to week 16. Key secondary endpoints included the

percentage of patients who achieved at least a 90% reduction in EASI (EASI 90), percentage of patients with at least 4-point improvement from baseline in Pruritus Numerical Rating Scale (Pruritus NRS), percentage of patients with at least 4-point improvement from baseline in Dermatology Life Quality Index (DLQI), and interference of itch on sleep (Sleep-Loss Scale). An additional secondary endpoint included the change from baseline in Patient Oriented Eczema Measure (POEM).

Subjects

Baseline characteristics

The demographic and baseline characteristics of the patients from ADvocate-1, ADvocate-2 and ADhere studies are presented in Table 2.

Table 1. Demographic and baseline characteristics by study

	ADvocate-1 N=424	**ADvocate-2 N=427**	**ADhere N=211**
Age (mean, years)	35.5	36.2	37.2
Adolescents (12 to 17 years) (%)	13.0	11.0	21.8
Elderly (≥65 years) (%)	7.3	7.7	9.5
Weight (mean, kg)	77.7	76.5	76.2
Female (%)	50.5	49.4	48.8
Race			
White (%)	68.2	59.3	61.6
Asian (%)	16.5	28.6	14.7
Black (%)	11.6	8.2	13.3
IGA of 3 (moderate AD) (%)	59.7	63.2	69.2
IGA of 4 (severe AD) (%)	40.3	36.8	30.8
Prior systemic treatment* (%)	54.0	55.5	47.4
EASI (mean)	29.6	29.7	27.3
Pruritus NRS (mean)	7.3	7.1	7.1
DLQI (mean)	15.4	15.5	14.4
Sleep-Loss Scale (mean)	2.3	2.2	2.0
POEM (mean)	20.8	20.8	19.5

*corticosteroids, cyclosporine, phototherapy and dupilumab (ADhere only)

Clinical response

Monotherapy studies (ADvocate-1 and ADvocate-2) – induction period, weeks 0-16

In ADvocate-1 and ADvocate-2, a significantly greater proportion of patients randomised to lebrikizumab 250 mg Q2W achieved IGA 0 or 1 with a ≥2-point improvement from baseline, EASI 75,

EASI 90, and an improvement of ≥4 points in Pruritus NRS compared to placebo at week 16 (see Table 3).

Table 2. Efficacy results of lebrikizumab monotherapy at week 16 in ADvocate-1 and ADvocate-2

	ADvocate-1		ADvocate-2	
	Week 16			
	Placebo N=141	LEB 250 mg Q2W N=283	Placebo N=146	LEB 250 mg Q2W N=281
IGA 0 or 1, %[a]	12.7	43.1*	10.8	33.2*
EASI 75, %[b]	16.2	58.8*	18.1	52.1*
EASI 90, %[b]	9.0	38.3*	9.5	30.7*
Pruritus NRS (≥4-point improvement), %[c]	13.0	45.9*	11.5	39.8*

LEB = lebrikizumab; N = number of patients
[a] Subjects with IGA 0 or 1 ("clear" or "almost clear") with a reduction of >2 points from baseline on a 0-4 IGA scale.
[b] Subjects with a 75% or 90% reduction in EASI from Baseline to Week 16, respectively.
[c] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥4.
*p<0.001 versus placebo.

In the two studies, fewer patients randomised to lebrikizumab needed rescue treatment (topical corticosteroids, systemic corticosteroids, immunosuppressants) as compared to patients randomised to placebo (14.7% versus 36.6%, respectively, across both studies).

Figure 1 and Figure 2 show the mean percent change from baseline in EASI and Pruritus NRS up to week 16.

Figure 1. Mean EASI percent change from baseline to week 16 in ADvocate 1 and 2

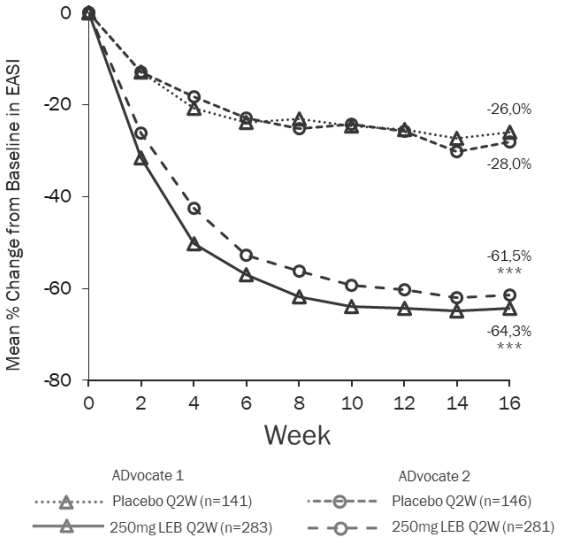
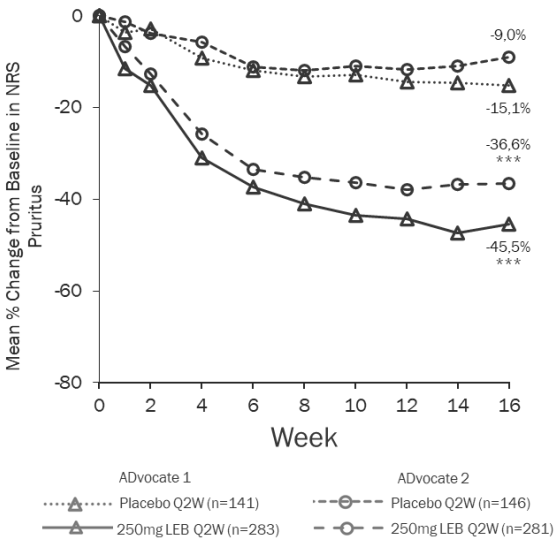


Figure 2. Mean pruritus NRS percent change from baseline to week 16 in ADvocate 1 and 2



***p<0.001 versus placebo

Treatment effects in subgroups (weight, age, gender, race, disease severity and prior use of systemic treatments) in ADvocate-1 and ADvocate-2 were consistent with the results in the overall study population during the induction phase.

Monotherapy studies (ADvocate-1 and ADvocate-2) – maintenance period, weeks 16-52

To evaluate maintenance of response, 157 subjects from ADvocate-1 and 134 subjects from ADvocate-2 treated with lebrikizumab 250 mg Q2W, who achieved IGA 0 or 1 or EASI 75 at week 16 without topical or systemic rescue treatment, were re-randomised in a blinded manner 2:2:1 to an additional 36-week treatment of (i) lebrikizumab 250 mg Q2W, or (ii) lebrikizumab 250 mg Q4W, or (iii) matching placebo for a cumulative 52-week study treatment (see Table 4).

Table 4. Efficacy results of lebrikizumab monotherapy in ADvocate-1 und ADvocate-2 at week 52 in subjects responding to treatment at week 16 in ADvocate-1 and ADvocate-2 (pooled analysis)

	ADvocate-1 and ADvocate-2 (pooled)		
	Week 52		
	Placebo[d] (LEB Withdrawal) N=60	LEB 250 mg Q2W N=113	LEB 250 mg Q4W N=118
IGA 0 or 1, %[a]	47.9	71.2*	76.9**
EASI 75, %[b]	66.4	78.4	81.7*
EASI 90, %[b]	41.9	64.0*	66.4**
Pruritus NRS (≥4-point improvement), %[c]	66.3	84.6	84.7

[a] Subjects with IGA 0/1 with a ≥2-point improvement from baseline at week 16 who continued to exhibit IGA 0/1 with a ≥2-point improvement at week 52.
[b] Subjects who achieved EASI 75 at week 16 and continued to exhibit EASI 75 at week 52, or subjects who achieved EASI 75 at Week 16 and exhibited EASI 90 at week 52, respectively.
[c] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥4.
[d] Subjects responding to lebrikizumab 250 mg Q2W at week 16 (IGA 0 or 1 or EASI 75) and re-randomised to placebo.
*p<0.05; **p<0.01 versus placebo.

Concomitant TCS Study (ADhere)

In ADhere, from baseline to week 16, a significantly greater proportion of patients randomised to and dosed with lebrikizumab 250 mg Q2W + TCS achieved IGA 0 or 1, EASI 75, and improvements of ≥4 points in the Pruritus NRS compared to placebo + TCS (see Table 5).

Table 5. Efficacy results of lebrikizumab combination therapy with TCS at week 16 in ADhere

	ADhere	
	Week 16	
	Placebo + TCS N=66	LEB 250 mg Q2W + TCS N=145

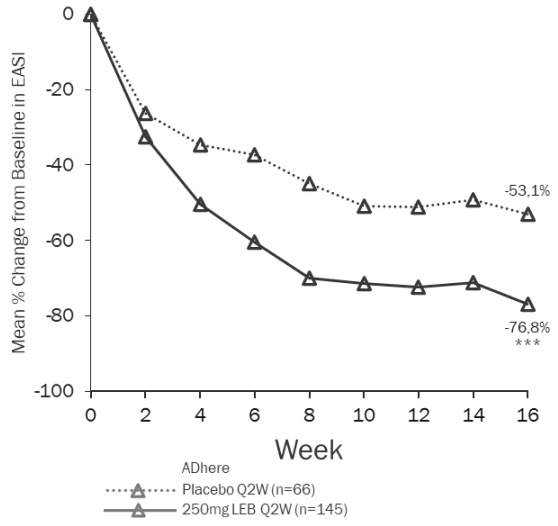
IGA 0 or 1, %[a]	22.1	41.2*
EASI 75, %[b]	42.2	69.5**
EASI 90, %[b]	21.7	41.2**
Pruritus NRS (≥4-point improvement), %[c]	31.9	50.6*

[a] Subjects with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points from baseline on a 0-4 IGA scale
[b] Subjects with a 75% or 90% reduction in EASI from Baseline to week 16, respectively.
[c] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥4.
*p<0.05; **p<0.001 versus placebo.

In ADhere, subjects who received lebrikizumab 250 mg Q2W+TCS from week 0 to 16 used TCS less often as compared to subjects who received placebo + TCS (1.4% and 4.5%, respectively).

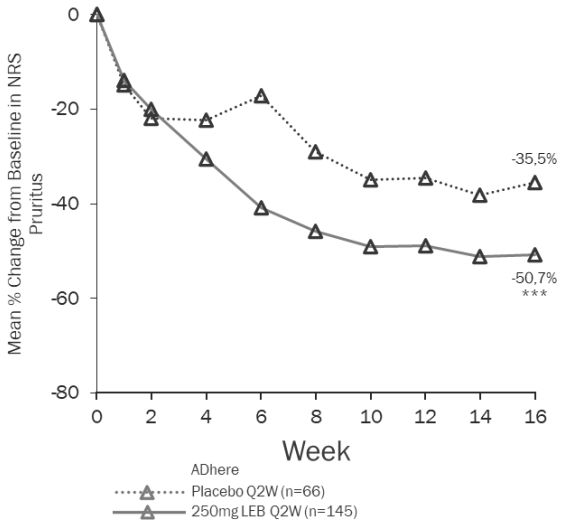
Figure 3 and Figure 4 show the mean percent change from baseline in EASI and the mean percent change from baseline in Pruritus NRS, respectively up to week 16.

Figure 3. Least squares mean percent change from baseline in EASI in ADhere



***p<0.001 versus placebo

Figure 4. Least squares mean percent change from baseline in Pruritus NRS in ADhere



***p<0.001 versus placebo

Treatment effects in subgroups (weight, age, gender, race, disease severity and prior use of systemic treatments) in ADhere were consistent with the results in the overall study population.
Subjects who responded at week 16 in ADhere and entered ADjoin and were treated with either lebrikizumab 250 mg Q2W or Q4W maintained their responses up to 56 weeks (75.4% and 86.8%, respectively, for IGA 0 or 1 and 85.6% and 81.2%, respectively, for EASI 75).

Patient-reported outcomes and health-related quality of life

In both monotherapy studies (ADvocate-1 and ADvocate-2) lebrikizumab 250 mg Q2W significantly improved patient-reported outcomes of disease severity (POEM), interference of itch on sleep (Sleep-Loss Scale), and health-related quality of life (DLQI) at week 16 compared to placebo. A significantly

greater proportion of patients administered lebrikizumab had clinically meaningful improvements in DLQI (defined as ≥4-point reduction from baseline), POEM and Sleep-Loss Scale from baseline to week 16 compared to placebo group (see Table 6).
In the TCS study (ADhere), lebrikizumab 250 mg Q2W + TCS improved interference of itch on sleep (Sleep-Loss Scale) and patient-reported disease severity (POEM) and health-related quality of life (DLQI) at week 16 compared to placebo + TCS (see Table 6).

Table 6. Patient-reported outcomes (health-related quality of life results) of lebrikizumab monotherapy at week 16 in ADvocate-1 and ADvocate-2, or with concomitant TCS at week 16 in ADhere

	ADvocate-1		ADvocate-2		ADhere	
	Week 16					
	Placebo N=141	LEB 250 mg Q2W N=283	Placebo N=146	LEB 250 mg Q2W N=281	Placebo + TCS N=66	LEB 250 mg Q2W + TCS N=145
DLQI (Adults) (≥4-point improvement), %[a]	33.8	75.6**	33.6	66.3**	58.7	77.4*
Sleep-Loss Scale (≥2-point improvement), %[b]	4.7	39.0**	8.2	28.0**	18.4	34.5*
POEM; LS mean change from baseline (±SE)	-3.9 (±0.72)	-11.3** (±0.47)	-3.5 (±0.77)	-9.5** (±0.52)	-6.24 (±1.04)	-10.23** (±0.73)

LS = least squares; SE = standard error
[a] Subjects with DLQI ≥4 points at baseline
[b] Subjects with Sleep-Loss Scale ≥2 points at baseline
*p<0.05; **p<0.001 versus placebo

Adolescents (12 to 17 years of age)

In the monotherapy studies ADvocate 1 and ADvocate 2, the mean age of adolescent patients was 14,6 years, the mean weight was 68.2 kg, and 56.9% were female. In these studies, 63.7% had a baseline IGA of 3 (moderate atopic dermatitis), 36.3% had a baseline IGA of 4 (severe atopic dermatitis), and 47.1% had received prior systemic treatment. In the concomitant study with TCS (Adhere), the mean age of adolescent patients was 14.6 years, mean weight was 62.2 kg, and 50.0% were female. In this study, 76.1% had a baseline IGA of 3 (moderate atopic dermatitis), 23.9% had a baseline IGA of 4 (severe atopic dermatitis), and 23.9% had received prior systemic treatment.
The efficacy results at week 16 in adolescent patients are presented in Table 7.

Table 7. Efficacy results of lebrikizumab monotherapy in ADvocate-1, ADvocate-2 and lebrikizumab combination therapy with TCS in ADhere at week 16 in adolescent patients

	ADvocate-1		ADvocate-2		ADhere	
	Week 16					
	Placebo N=18	LEB 250 mg Q2W N=37	Placebo N=17	LEB 250 mg Q2W N=30	Placebo + TCS N=14	LEB 250 mg Q2W + TCS N=32
IGA 0 or 1, %[a]	22.2	48.6	5.9	44.1**	28.6	57.3
EASI 75, %[a]	22.2	62.2**	12.0	61.7**	57.1	88.0*
EASI 90, %[a]	16.7	45.9*	6.1	34.3*	28.6	55.1
Pruritus NRS (≥4-point improvement), %[b]	22.8	54.3*	0.3	42.1	13.8	45.8

[a] At Week 16, subjects with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points from baseline on a 0-4 IGA scale, or a 75% or 90% reduction in EASI from baseline to week 16, respectively.
[b] The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥4.
*p<0.05; **p<0.01 versus placebo.

Adolescent patients treated with lebrikizumab and lebrikizumab + TCS achieved clinically meaningful improvements in disease severity and maintained response up to week 52. Additional data from the single-arm ADore study with lebrikizumab in 206 adolescents support the efficacy of lebrikizumab in adolescent patients up to 52 weeks of treatment.

Pharmacokinetics

Absorption

After a subcutaneous dose of 250 mg lebrikizumab, peak serum concentrations were achieved approximately 7 to 8 days post dose.
Following the 500 mg loading doses 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, the predicted steady-state trough concentrations ($C_{trough,ss}$) following lebrikizumab 250 mg Q2W and Q4W subcutaneous dosing in patients with atopic dermatitis (median and 5^{th}-95^{th} percentile) were 87 (46-159) µg/mL and 36 (18-68) µg/mL, respectively.
The absolute bioavailability was estimated at 86% based on a population PK analysis. Injection site location had no relevant influence on the absorption of lebrikizumab.

Distribution

Based on a population PK analysis, the total volume of distribution at steady-state was 5.14 L.

Metabolism

Metabolism studies were not conducted because lebrikizumab is a protein. Lebrikizumab is expected to degrade to small peptides and individual amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

In the population PK analysis, clearance was 0.154 L/day and was independent of dose. The mean elimination half-life was approximately 24.5 days.

Linearity/non-linearity

Lebrikizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure over a dose range of 37.5 to 500 mg given as a subcutaneous injection in patients with AD or in healthy volunteers.

Kinetics in specific patient groups

Gender, age, and race

Gender, age (range 12 to 93 years), and race (64% Caucasian, 15% Black/African American, 16% Asian and 6% Other) did not have a significant effect on the pharmacokinetics of lebrikizumab.

Hepatic and renal impairment

Specific clinical pharmacology studies to evaluate the effects of hepatic or renal impairment on the pharmacokinetics of lebrikizumab have not been conducted. Lebrikizumab, as a monoclonal antibody, is not expected to undergo significant renal or hepatic elimination. The population PK analyses included 54 (3%) subjects with elevated liver enzymes ALT or AST ≥1.5 x ULN at baseline and 347 (22%) subjects with impaired renal function (glomerular filtration rate between 30 and 89 mL/min) at baseline. Population PK analyses show that markers of hepatic or renal function did not affect the pharmacokinetics of lebrikizumab.

Body weight

Exposure to lebrikizumab was lower in the 10% of subjects with higher body weight (≥100 kg).

Children and adolescents

Based on population PK analysis adolescents 12 to 17 years of age with atopic dermatitis had slightly higher lebrikizumab serum trough concentrations compared to adults, which was related to their lower body weight distribution.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity (including safety pharmacology endpoints) and toxicity to reproduction and development.

Genotoxicity

The mutagenic potential of lebrikizumab has not been evaluated; however monoclonal antibodies are not expected to alter DNA or chromosomes.

Cancerogenicity

Cancerogenicity studies have not been conducted with lebrikizumab. Evaluation of the available evidence related to IL-13 inhibition and animal toxicology data with lebrikizumab does not suggest cancerogenic potential for lebrikizumab.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the container.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Store in the original packaging in order to protect the contents from light.
Keep out of the reach of children.
After removal from the refrigerator, store Ebglyss not above 30°C and use within 7 days or discard.
Once stored out of refrigeration, do not place back in the refrigerator.

Instructions for handling

The instructions for the preparation and administration of Ebglyss in a pre-filled syringe or in a pre-filled pen are given at the end of the package leaflet.
The solution should be clear to opalescent, colourless to slightly yellow to slightly brown solution and free from visible particulates. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used.
After removing the 250 mg pre-filled syringe or pre-filled pen from the refrigerator, it should be allowed to reach room temperature by waiting for 45 min before injecting Ebglyss.

The pre-filled syringe or the pre-filled pen should not be exposed to heat or direct sunlight and should not be shaken.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

69344, 69460 (Swissmedic)

Packs

Ebglyss, solution for injection in pre-filled syringe

1 pre-filled syringe [B]
2 pre-filled syringes [B]

Ebglyss, solution for injection in pre-filled pen

1 pre-filled pen [B]
2 pre-filled pens [B]

Marketing authorisation holder

Almirall AG, 8304 Wallisellen

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April 2024