1. NAME OF THE MEDICINAL PRODUCT

Ebglyss

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ebglyss 250 mg 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).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 who are candidates for systemic therapy.

4.2 Posology and method of administration

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

Posology

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. Some patients with initial partial response may further improve with continued treatment every other week up to week 24.

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.

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 populations

Elderly (≥ 65 years)
No dose adjustment is recommended for elderly patients (see section 5.2).

Renal and hepatic impairment
No dose adjustment is recommended for patients with renal or hepatic impairment (see section 5.2).

Body weight
No dose adjustment for body weight is recommended (see section 5.2).

Paediatric population

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

Method 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 healthcare professional 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 section 4.8).

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if lebrikizumab will influence the immune response against helminth infections by inhibiting IL-13 signalling.

Patients with pre-existing helminth infections should be treated before initiating treatment with lebrikizumab. If patients become infected while receiving lebrikizumab and do not respond to antihelminth treatment, treatment with lebrikizumab should be discontinued until infection resolves.

Vaccinations

Prior to initiating therapy with lebrikizumab, it is recommended that patients are brought up to date with 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 section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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.

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. 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) and immune responses 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. Therefore, patients receiving lebrikizumab may receive concurrent inactivated or non-live vaccinations. For information on live vaccines see section 4.4.

Concomitant therapies

Given that lebrikizumab is a monoclonal antibody, no pharmacokinetic interactions are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of lebrikizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of lebrikizumab during pregnancy.

Breast-feeding

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 newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from lebrikizumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lebrikizumab has no or negligible influence on the ability to drive and use machines.

4.8 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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 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 selected adverse reactions

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%).
During maintenance treatment period (16-52 weeks) the incidence of conjunctivitis and conjunctivitis allergic with lebrikizumab was 5.0% and 5.9% respectively.
Across all clinical studies, among lebrikizumab-treated patients treatment discontinuation due to conjunctivitis and conjunctivitis allergic occurred in 0.7% and 0.3% of cases, respectively. Severe cases of conjunctivitis and conjunctivitis allergic occurred in 0.1% and 0.2% of cases, respectively. 72% of patients recovered, of those 57% recovered within 90 days.

Eosinophilia

Lebrikizumab-treated patients had a greater mean increase from baseline in eosinophil count compared to patients treated with placebo. In lebrikizumab treated patients 20.3% had any increase in eosinophil count compared to 11.7% with placebo. In general, the increase in the lebrikizumab-treated patients was mild or moderate and transient. Eosinophilia ≥5000 cells/mcL was observed in 0.4% lebrikizumab-treated patients and none of the placebo-treated patients. Adverse reactions of eosinophilia were reported in 0.6% of patients treated with lebrikizumab and with a similar rate in patients treated with placebo during the initial treatment period. Eosinophilia did not result in treatment discontinuation and no eosinophil-related disorders were reported.

Injection site reactions

Injection site reactions (including pain and erythema) 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.

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 of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 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 overdose, the patient should be monitored for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other dermatological preparations, agents for dermatitis, excluding corticosteroids , 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 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. Inhibition of IL-13 signalling is expected to be of benefit in diseases in which IL-13 is a key contributor to the disease pathogenesis. Lebrikizumab does not prevent the binding of IL-13 to the IL-13 receptor alpha 2 (IL-13Rα2 or decoy receptor), which allows the internalisation of IL-13 into the cell.

Pharmacodynamic effects

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.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Clinical efficacy and safety

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.

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 Q2W; (ii) lebrikizumab 250 mg every 4 weeks (Q4W); or (iii) matching placebo up to 52 weeks.

In ADvocate-1 and 2, patients not achieving IGA 0 or 1 or EASI 75 at week 16, or who received rescue medication prior to week 16, were entered into an Escape Arm and treated with open-label lebrikizumab 250 mg Q2W through Week 52.

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 EASI 75 from baseline to week 16. Key secondary endpoints (adjusted for multiplicity) 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), which is a patient-reported, single-item, daily scale measuring the extent of interference of itch on sleep over the last night on a 5-point Likert scale. An additional secondary endpoint (not adjusted for multiplicity) included the change from baseline in Patient Oriented Eczema Measure (POEM).

Subjects

Baseline characteristics
The monotherapy studies ADvocate-1 and ADvocate-2 enrolled 424 and 427 patients, respectively, and across studies the mean age was 35.8, the mean weight was 77.1 kg, 49.9% were female, 63.7% were white, 22.6% were Asian, and 9.9% were black, 12.0% were adolescents (12 to 17 years). Overall, 61.5% of patients had a baseline IGA of 3 (moderate atopic dermatitis), 38.5% of patients had a baseline IGA of 4 (severe atopic dermatitis), and 54.8% of patients had received prior systemic treatment. The mean baseline EASI was 29.6, the mean baseline Pruritus NRS was 7.2 and the mean baseline DLQI was 15.5.

The concomitant TCS study ADhere enrolled 211 patients and the mean age was 37.2, the mean weight was 76.2 kg, 48.8% were female, 61.6% were white, 14.7% were Asian, and 13.3% were black, 21.8% were adolescents. In this study, 69.2% of patients had a baseline IGA of 3 (moderate atopic dermatitis), 30.8% of patients had a baseline IGA of 4 (severe atopic dermatitis), and 47.4% of patients had received prior systemic treatment. The mean baseline EASI was 27.3, the mean baseline Pruritus NRS was 7.1 and the mean baseline DLQI was 14.4.

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 and DLQI compared to placebo at week 16 (see Table 2).

In both monotherapy studies, lebrikizumab reduced daily worst itch severity compared to placebo, as measured by the percent change from baseline in Pruritus NRS, already at week 1 of treatment. The improvement in Pruritus NRS occurred in conjunction with improvements in skin inflammation related to atopic dermatitis and quality of life.

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***
DLQI (Adults) (≥ 4-point improvement), %[d]	33.8	75.6***	33.6	66.3***

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.
[d] The percentage is calculated relative to the number of subjects with a baseline DLQI ≥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).

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 3).

Table 3. Efficacy results of lebrikizumab monotherapy 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 Q4W N=118
IGA 0 or 1, %[a]	47.9	76.9**
EASI 75, %[b]	66.4	81.7*
EASI 90, %[b]	41.9	66.4**
Pruritus NRS (≥ 4-point improvement), %[c]	66.3	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.

Among subjects who received lebrikizumab during the induction period and continued lebrikizumab 250 mg Q2W open-label treatment up to week 52 in the Escape Arm, 58% achieved EASI 75 and 28% achieved IGA 0 or 1 with a ≥2-point improvement from baseline at week 52 in ADvocate-1 and ADvocate-2 (pooled).

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 and DLQI compared to placebo + TCS (see Table 4).

Table 4. 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*
DLQI (Adults) (≥ 4-point improvement), %[d]	58.7	77.4*

[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.
[d] The percentage is calculated relative to the number of subjects with a baseline DLQI ≥4.
* p<0.05; **p<0.01; *** p<0.001 versus placebo.

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

Subjects who responded at week 16 in ADhere and entered ADjoin were treated with lebrikizumab 250 mg Q4W maintained their responses up to 56 weeks (86.8% for IGA 0 or 1 and 81.2% for EASI 75).

Other patient-reported outcomes

In both monotherapy studies (ADvocate-1 and ADvocate-2) and in the concomitant TCS study (ADhere) lebrikizumab 250 mg Q2W significantly improved POEM and interference of itch on sleep (Sleep-Loss Scale) at week 16 compared to 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 5.

Table 5. 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.

5.2 Pharmacokinetic properties

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 did not significantly influence the absorption of lebrikizumab.

Distribution

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

Biotransformation

Specific 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.

Special populations

Gender, age, and race

Gender, age (range 12 to 93 years), and race did not have a significant effect on the pharmacokinetics of lebrikizumab.

Renal and hepatic impairment

Specific clinical pharmacology studies to evaluate the effects of renal or hepatic 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. Population PK analyses show that markers of renal or hepatic function did not affect the pharmacokinetics of lebrikizumab.

Body weight

Exposure to lebrikizumab was lower in subjects with higher body weight but this had no meaningful impact on clinical efficacy.

Paediatric population

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.

5.3 Preclinical safety 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.

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

Carcinogenicity 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 carcinogenic potential for lebrikizumab.

No effects on fertility parameters were observed in sexually mature monkeys after a long-term intravenous (females) or subcutaneous (males) treatment with lebrikizumab. Lebrikizumab had no effects on embryo-fetal or postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L-Histidine
Glacial acetic acid
Polysorbate 20
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

After removal from the refrigerator, Ebglyss must be used within 7 days (at a temperature up to 30°C) or discarded. Once stored out of refrigeration, do not place back in the refrigerator.

6.5 Nature and contents of container

2 mL solution in a 2.25 mL Type-1 clear glass syringe in a pre-filled pen with extra-small round flange, with a 27 gauge special thin wall x 8 mm stacked stainless steel needle, and closed with a laminated bromobutyl elastomeric plunger and a rigid needle shield.

Pack size:1 pre-filled pen

6.6 Special precautions for disposal and other handling

Detailed instructions for administration of Ebglyss 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 pen from the refrigerator, it should be allowed to reach room temperature by waiting for 45 min before injecting Ebglyss.

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.

7. LICENSE HOLDER

Eli Lilly Israel Ltd.
4 HaSheizaf St., POB 4246 Ra'anana 4366411, Israel

8. MANUFACTURER

Eli Lilly and Company,
Lilly Corporate Center,
Indianapolis, IN 46285, United States

9. LICENSE NUMBER

177-68-38066-00

Approved on November 2024.

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