Iowa PDL New Drug Review

Proprietary Name: Ebglyss®
Common Name: lebrikizumab-lbkz
PDL Category: Anti-IgE & Anti-Interleukin Antibodies

Pharmacology/Usage: Lebrikizumab-lbkz, the active ingredient of Ebglyss®, is an interleukin (IL)-13 antagonist, an immunoglobulin G4 (IgG4) monoclonal antibody that binds to IL-13 and inhibits IL-13 signaling. It is an IgG4 monoclonal antibody that binds with high affinity and slow off-rate to IL-13 and allows IL-13 to bind to IL-13Rα1 but inhibits human IL-13 signaling through the IL-4Rα/IL-13Rα1 receptor complex. IL-13 is a naturally occurring cytokine that is involved in Type 2 inflammation, which is an important component in the pathogenesis of atopic dermatitis. Lebrikizumab-lbkz inhibits IL-13 induced responses including the release of proinflammatory cytokines, chemokines and IgE. Lebrikizumab-lbkz-bound IL-13 can still bind IL-13Rα2 allowing subsequent internalization and natural clearance of IL-13.

Indication: For the treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Ebglyss® can be used with or without topical corticosteroids.

There is no pregnancy category for this medication; however, the risk summary indicates that available data on use in pregnant women are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Transport of human IgG antibody across the placenta increases as pregnancy progresses and peaks during the third trimester; thus, lebrikizumab-lbkz may be transmitted from the mother to the developing fetus. Report pregnancies to Eli Lilly and Company at 1-800-LillyRx. The safety and efficacy of use have not been established in pediatric patients younger than 12 years of age and pediatric patients 12 years and older who weigh less than 40kg.

Dosage Form: Solution for Injection, preservative free, available as:

- 250mg/2ml in a single-dose prefilled pen.
- 250mg/2ml in a single-dose prefilled syringe with needle shield.

Recommended Dosage: Complete all age-appropriate vaccinations per current immunization guidelines prior to administration of Ebglyss®.

The recommended dosage is an initial dose of 500mg (two 250mg injections) at week 0 and week 2, followed by 250mg every 2 weeks until week 16 or later, when adequate clinical response is achieved. The maintenance dosage is 250mg every 4 weeks.

Ebglyss® can be used with or without topical corticosteroids (TCS). Topical calcineurin inhibitors (TCI) may be used, but reserved for sensitive areas only, such as the face, neck, intertriginous and genital areas.

Important administration instructions:

- Ebglyss® is for subcutaneous (SC) administration.

- Ebglyss® is intended for use under the guidance of a healthcare professional. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of Ebglyss®. Adults may self-inject, or caregivers may give Ebglyss® after training in SC injection technique. For pediatric patients, caregivers may give injections after training in SC injection technique.
- Sites for injection include the abdomen, thigh, and back of the upper arm. Administration in the back of the upper arm may be performed by a caregiver or healthcare provider.
- Alternate the injection site with each injection. Do not inject within 2 inches of the navel or into areas where the skin is tender, bruised, red, hard, or in an area of the skin that is affected by atopic dermatitis or skin lesions.
- Remove Ebglyss® from the refrigerator before injection. If using:
    - Ebglyss® prefilled pen, it is not necessary to warm up to room temperature before use.
    - Ebglyss® prefilled syringe, leave at room temperature for 45 minutes without removing the needle cap.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ebglyss®) minus reported % incidence for placebo in monotherapy study through week 16. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included conjunctivitis (7%), injection site reactions (2%), and herpes zoster (<1%).

Hypersensitivity reactions have been reported with the use of Ebglyss®. If a serious hypersensitivity reaction occurs, discontinue Ebglyss® and start appropriate therapy.

Conjunctivitis and keratitis adverse reactions have been reported in clinical trials, both of which occurred more frequently in atopic dermatitis subjects who received Ebglyss® compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered during the treatment period. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

Patients with known helminth infections were excluded from participating in clinical studies. It is not known if Ebglyss® will influence the immune response against helminth infections by inhibiting IL-13 signaling. Treat patients with preexisting helminth infections before starting Ebglyss® treatment. If patients become infected while receiving Ebglyss® and do not respond to antihelminth treatment, discontinue treatment with Ebglyss® until the infection resolves.

Ebglyss® may alter a patient's immunity and increase the risk of infection following administration of live vaccines. Prior to therapy with Ebglyss®, complete all age-appropriate vaccinations per current immunization guidelines. Avoid use of live vaccines immediately prior to or during treatment with Ebglyss®. No data are available on the response to live vaccines.

Contraindications: In patients with prior serious hypersensitivity to lebrikizumab-lbkz or any excipients of the product.

Manufacturer: Eli Lilly & Company

Analysis: Three multicenter, randomized, double-blind, placebo-controlled trials were performed (ADvocate 1, ADvocate 2, and ADhere) to assess the efficacy of Ebglyss® and which enrolled subjects 12 years of age and older (N=1062) with moderate to severe atopic dermatitis (AD) not adequately controlled by topical medication(s) and who were candidates for systemic therapy. Disease severity was defined by an Investigator's Global Assessment

(IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%.

A total of 148 subjects (14%) were 12 to <18 years of age who weighed at least 40kg and 914 patients (86%) were adults. At baseline, 50% of subjects were male, 63% were white, 63% had a baseline IGA score of 3 (moderate AD), and 37% had a baseline IGA score of 4 (severe AD). The baseline mean EASI was 29 and the baseline Pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10. Of all subjects, 99% had received prior treatment for AD.

In all 3 trials, subjects in the Ebglyss® group received subcutaneous injections of Ebglyss® 500mg at week 0 and week 2, followed by 250mg Q2W through week 16. To assess the maintenance and durability of response in the monotherapy trials (ADvocate 1 and ADvocate 2), subjects originally randomized to Ebglyss® who achieved an IGA score of 0 or 1, or at least a 75% reduction in EASI from baseline (EASI-75) at week 16 and did not require rescue therapy were re-randomized to an additional 36 weeks of either a maintenance dose of Ebglyss® 250mg Q2W, Ebglyss® 250mg Q4W, or placebo. Subjects who did not achieve IGA 0 or 1 or EASI-75 at week 16 or subjects who required rescue therapy during the first 16 weeks were treated with open-label Ebglyss® 250mg Q2W.

In the concomitant therapy trial (ADhere), subjects received Ebglyss® plus TCS or placebo plus TCS. Topical calcineurin inhibitors were permitted for sensitive areas only.

All three trials assessed the primary endpoint, the proportion of subjects who achieved an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline at week 16. Other outcomes assessed at week 16 included the proportion of subjects with EASI-75 and EASI-90, and improvement in itch severity as defined by a reduction of at least 4 points on an 11-point Pruritus NRS. ADvocate 1 and ADvocate 2 also assessed the maintenance and durability of response through week 52. The results of the monotherapy trials are presented in the table below, which was adapted from the prescribing information.

	ADvocate 1			ADvocate 2		
	Ebglyss®	**Placebo**	**Difference from placebo**	**Ebglyss®**	**Placebo**	**Difference from placebo**
Number of subjects	283	141		281	146	
IGA 0 or 1 (primary endpoint)	43%	13%	30%	33%	11%	22%
NNT *calculated by Optum Rx*	4			5		
EASI-75	59%	16%	42%	52%	18%	33%
EASI-90	38%	9%	29%	31%	10%	21%
# of subjects with baseline Pruritus NRS score ≥4	263	130		253	134	
Pruritus NRS ≥4 point improvement	46%	13%	33%	40%	12%	28%

The results in the concomitant therapy trial (ADhere) at week 16, where subjects received Ebglyss® plus TCS or placebo plus TCS were consistent with the results in the monotherapy trials.

Maintenance and durability of response (week 16 to week 52) were assessed. Ebglyss®-treated subjects achieving IGA 0 or 1 or EASI-75, and who did not receive rescue therapy at week 16, were re-randomized to 36 weeks of maintenance treatment with Ebglyss® 250mg Q2W, Ebglyss® 250mg Q4W, or placebo in ADvocate 1 and ADvocate 2. Results are presented in the table below, which was adapted from the prescribing information.

	ADvocate 1			ADvocate 2		
	Ebglyss® 250mg Q2W	Ebglyss® 250mg Q4W	Placebo	Ebglyss® 250mg Q2W	Ebglyss® 250mg Q4W	Placebo
# of subjects who were IGA 0 or 1 responders at wk 16	45	45	22	32	32	16
IGA of 0 or 1 at week 52	76%	74%	47%	65%	81%	50%
# of subjects who were EASI-75 responders at wk 16	61	62	30	51	53	27
EASI-75 at week 52	79%	79%	61%	77%	85%	72%

Place in Therapy: Ebglyss® is an IL-13 antagonist indicated for the treatment of adults and pediatric patients 12 years of age and older who weigh at least 40kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Ebglyss® can be used with or without topical corticosteroids. Prior to starting treatment, complete all age-appropriate vaccinations per current immunization guidelines. Three studies assessed the safety and efficacy of Ebglyss® in patients with moderate-to-severe atopic dermatitis, two of which were monotherapy studies and one was a concomitant therapy trial where both Ebglyss® and placebo treatment groups also utilized TCS. All three trials assessed the primary endpoint of the proportion of subjects who achieved an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline at week 16. More in the Ebglyss® groups achieved the primary endpoint as compared to the placebo groups. Per the full-text study by Silverberg et al[2] (of ADvocate 1 and ADvocate 2), the results of the primary endpoint were statistically significant for both studies, in favor of the Ebglyss® group ($p<0.001$ for both studies). Per the full-text study by Simpson et al[3] of the ADhere study, significantly more in the lebrikizumab plus TCS group achieved IGA score of 0 or 1 with 2 or more points improvement from baseline as compared with the placebo plus TCS group at week 16 (41.2% vs 22.1%, respectively; $p=0.01$). Direct head-to-head active comparator studies were not currently found.

Summary

There is some evidence from a phase 3 study to suggest that Ebglyss® plus topical corticosteroids may be more effective than placebo plus topical corticosteroids for the primary endpoint of the proportion of subjects who achieved an IGA score of 0 or 1 and at least a 2-point improvement from baseline at week 16. It is recommended that Ebglyss® be available as a preferred option and require prior authorization to confirm appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Non-Preferred**
- ☒ **Preferred with Conditions**

References

[1] Ebglyss [package insert]. Indianapolis, IN: Eli Lilly and Company; 2024.

[2] Silverberg JI, Guttman-Tassky E, Thaci D, et al. Two phase 3 trials of lebrikizumab for moderate-to-severe atopic dermatitis. *NEJM.* 2023; 388(12): 1080-1091.

[3] Simpson EL, Gooderham M, Wollenberg A, et al. Efficacy and safety of lebrikizumab in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis: A randomized clinical trial (ADhere). *JAMA Dermatol.* 2023; 159(2): 182-191.

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