NEW DRUG APPROVAL

Brand Name	Adbry™
Generic Name	tralokinumab-ldrm
Drug Manufacturer	Leo Pharma A/S

New Drug Approval

FDA Approval Date: December 27, 2021

Review designation: N/A

Type of review: Biologic License Application 761180

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Atopic dermatitis (AD), which is a specific form of eczema, is the most common chronic inflammatory skin disease. This chronic disorder associated with pruritus usually starts in infancy and presents with dry skin, eczematous lesions and lichenification. It is believed that AD is associated with other IgE associated disorders like allergic rhinitis, asthma, and food allergies. AD has significant morbidity, and it appears that the prevalence of the disorder has been increasing over the past few decades. Atopic dermatitis has a complex etiology including genetic and environmental factors which lead to abnormalities in the epidermis and the immune system. Atopic dermatitis is part of the atopic triad (atopic dermatitis, allergic rhino conjunctivitis, and asthma) which may start simultaneously or in succession in what is known as the "atopic march." Patients with the atopic triad have a defective barrier of the skin, upper respiratory, and lower respiratory tract which leads to their symptomatology. If one parent is atopic, there is more than a 50% chance that their offspring will develop atopic symptoms. If both parents are affected, up to 80% of offspring will be affected. Genetic alterations include loss of function mutations of filaggrin (Filament Aggregating Protein), an epidermal protein that is broken down into natural moisturization factor. Filaggrin mutations are present in up to 30% of atopic dermatitis patients and may also predispose patients to ichthyosis vulgaris, allergic rhinitis, and keratosis pilaris. Food hypersensitivity may also cause or exacerbate atopic dermatitis in 10% to 30% of patients. Ninety percent of such reactions or flares are caused by eggs, milk, peanuts, soy, and wheat.

Atopic dermatitis is seen in approximately 10% to 30% of children and 2% to 10% of adults in developed countries. This prevalence has increased two to three-fold in recent decades. Atopic dermatitis has a higher incidence at higher latitudes, which may be related to decreased sun exposure and lower humidity levels. Atopic dermatitis is divided into three subsets based on the age of onset:

- Early-onset atopic dermatitis (birth to 2 years old): most common type of atopic dermatitis, with approximately 60% of cases starting by age 1. Sixty percent of cases resolve by 12 years old.
- Late-onset atopic dermatitis: symptoms begin after the onset of puberty.
- Senile onset atopic dermatitis: an unusual subset with onset in patients older than 60 years old.

Efficacy

The efficacy of Adbry™ was assessed in three randomized, double-blind, placebo-controlled trials [ECZTRA 1 (NCT03131648), ECZTRA 2 (NCT03160885), and ECZTRA 3 (NCT03363854)]. Efficacy was assessed in a total of 1934 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by

topical medication(s). 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 (BSA) involvement of ≥10%. At baseline, 58% of subjects were male, 69% of subjects were White, 50% of subjects had a baseline IGA score of 3 (moderate AD), and 50% of subjects had a baseline IGA score of 4 (severe AD). The baseline mean EASI score was 32 and the baseline weekly averaged Worst Daily Pruritus Numeric Rating Scale (NRS) was 8 on a scale of 0-10.

Table 1. Clinical Trial Results Summary

Efficacy Results: Initial 16-Week Period – Adbry Q2W vs. Placebo			
	ECZTRA 1 (N = 802[a])	**ECZTRA 2 (N = 794[a])**	**ECZTRA 3 (N = 380[a])**
Primary endpoint: IGA 0 or 1 at Week 16	16% vs. 7% for placebo (difference: 9%; 95% CI, 4–13)	21% vs. 9% for placebo (difference: 12%; 95% CI, 7–17)	38% vs. 27% for placebo (difference: 11%; 95% CI, 1–21)
Primary endpoint: EASI-75 at Week 16	25% vs. 13% for placebo (difference: 12%; 95% CI, 6–18)	33% vs. 10% for placebo (difference: 22%; 95% CI, 17–28)	56% vs. 37% for placebo (difference: 20%; 95% CI, 9–30)
Key secondary endpoint: Worst Daily Pruritus NRS (≥4-point reduction) at Week 16	20% vs. 10% for placebo (difference: 10%; 95% CI, 4–15)	25% vs. 9% for placebo (difference: 16%; 95% CI, 11–21)	46% vs. 35% for placebo (difference: 11%; 95% CI, 1–22)
Efficacy Results: Maintenance Period – Adbry Q2W and Adbry Q4W (vs. Placebo in ECZTRA 1 and ECZTRA 2)			
	ECZTRA 1[b] (N = 179)	**ECZTRA 2[b] (N = 218)**	**ECZTRA 3[b] (N = 131)**
Secondary endpoint: IGA 0 or 1 at Week 52 (Week 32 for ECZTRA 3)	51% Q2W and 39% Q4W vs. 47% placebo	60% Q2W[c] and 50% Q4W vs. 23% placebo	89% Q2W and 76% Q4W
Secondary endpoint: EASI-75 at Week 52 (Week 32 for ECZTRA 3)	60% Q2W and 49% Q4W vs. 33% placebo	57% Q2W[d] and 55% Q4W[c] vs. 20% placebo	92% Q2W and 90% Q4W
Safety Results			

• Common adverse events (incidence ≥1% and greater than placebo) were upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia.
• In the initial 16-weeks of the ECZTRA 1 and ECZTRA 2 trials, 0.7% of subjects in the Adbry group discontinued treatment due to ARs compared with 0% in the placebo group. Discontinuation rates were similar in ECZTRA 3.
• In Weeks 16–52 of ECZTRA 1 and ECZTRA 2 and Weeks 16–32 of ECZTRA 3:
  ○ The safety profile of Adbry was consistent with that in the initial 16 weeks.
  ○ The frequency of ARs with Adbry 300 mg Q2W and Q4W in ECZTRA 1 and ECZTRA 2 was 44% and 34%, respectively, and 43% and 26% with Adbry 300 mg + TCS Q2W and Q4W in ECZTRA 3, respectively.		

Sources: Adbry Prescribing Information, NCT03131648 (ECZTRA 1), NCT03160885 (ECZTRA 2), NCT03363854 (ECZTRA 3).

Abbreviations: ARs, adverse reactions; CI, confidence interval, EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, Numeric Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroid.

a. The number shown is the number of patients randomized in the trial. The efficacy results were based on the number of patients randomized and dosed, referred to as the full analysis set (FAS). The FAS for ECZTRA1, ECZTRA 2, and ECZTRA 3 was 798, 792, and 378 subjects, respectively.

b. Of the patients in the Adbry group who achieved IGA scores of 0 or 1 and/or EASI-75 at Week 16, the proportion whose response was maintained without any rescue therapy use at Week 52 (Week 32 in ECZTRA 3).

c. P <0.01 versus placebo.

d. P <0.001 versus placebo.

Safety

ADVERSE EVENTS

Most Common Adverse Reactions (Incidence ≥1% and Greater Than Placebo)

Initial 16-week trial period (Adbry™ monotherapy vs. placebo; Adbry™+ TCS vs. placebo):

• Upper respiratory tract infections (23.8% vs. 20.4%; 30% vs. 15.4%)

• Conjunctivitis (7.5% vs. 3.1%; 13.6% vs. 4.9%)

• Injection site reactions (7.4% vs. 4.1%; 11.1% vs. 0.8%)

• Eosinophilia (1.4% vs. 0.5%; 1.2% vs. 0%) Weeks 16–52: Safety profile consistent with that in the initial 16-week treatment period.

WARNINGS & PRECAUTIONS

Hypersensitivity-

Hypersensitivity reactions including anaphylaxis and angioedema, have been reported with use of Adbry™. If a serious hypersensitivity reaction occurs, discontinue immediately and initiate appropriate therapy.

Conjunctivitis and Keratitis-

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received Adbry™. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Parasitic (Helminth) Infections-

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if Adbry™ will influence the immune response against helminth infections by inhibiting IL-13 signaling. Treat patients with pre-existing helminth infections before initiating treatment with Adbry™. If patients become infected while receiving Adbry™ and do not respond to antihelminth treatment, discontinue treatment with Adbry™ until the infection resolves.

Risk of Infection with Live Vaccines-

Adbry™ may alter a patient's immunity and increase the risk of infection following administration of live vaccines. Prior to initiating therapy, complete all age-appropriate vaccinations according to current immunization guidelines. Avoid use of live vaccines in patients treated with Adbry™. Limited data are available regarding coadministration of Adbry™ with non-live vaccines.

CONTRAINDICATIONS

Contraindicated in patients who have known hypersensitivity to tralokinumab-ldrm or any excipients in Adbry™.

Clinical Pharmacology

MECHANISMS OF ACTION

Tralokinumab is a human IgG4 monoclonal antibody that specifically binds to human interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptor alpha1 and alpha2 subunits (IL-13R alpha1 and IL-13R alpha2). IL-13 is a naturally occurring cytokine of the Type 2 immune response. Tralokinumab inhibits the bioactivity of IL-13 by blocking IL-13 interaction with IL-13R alpha1/IL-4R alpha receptor complex. Tralokinumab inhibits IL-13-induced responses, including the release of proinflammatory cytokines, chemokines and IgE

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Dose & Administration

ADULTS

600 mg (four 150-mg injections) subcutaneously initially, followed by 300 mg (two 150-mg injections) subcutaneously every other week. After 16 weeks of treatment, for patients weighing less than 100 kg who achieve clear or almost clear skin, a dosage of 300 mg subcutaneously every 4 weeks may be considered. Tralokinumab-ldrm can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

PEDIATRICS

None

GERIATRICS

None

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 150 mg/mL solution in a single-dose prefilled syringe with needle guard.