Tralokinumab-ldrm (Adbry™) New Drug Update

January 2022

Nonproprietary Name	tralokinumab-ldrm
Brand Name	Adbry
Manufacturer	Leo
Form	Single-dose, prefilled syringe
Strength	150 mg/mL
FDA Approval	December 27, 2021
Market Availability	Expected by February 2022
FDA Approval Classification	Standard Review
FDB Classification- Specific Therapeutic Class (HIC3)	Interleukin-13 (IL-13) inhibitors – MAB (V4G)

INDICATION[1]

Tralokinumab-ldrm (Adbry) is an interleukin-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable; can be used with or without topical corticosteroids.

PHARMACOKINETICS

After a 600 mg tralokinumab-ldrm loading dose, followed by 300 mg every other week, maximum concentration (Cmax) was reached 5 to 8 days after administration with a steady-state concentration achieved by week 16. The mean volume of distribution was estimated to be approximately 4.2 L. Tralokinumab-ldrm is metabolized into small peptides by catabolic pathways with an elimination half-life of 3 weeks. The exposure of tralokinumab-ldrm decreases with increasing body weight, specifically > 100 kg. The half-life ($t_{1/2}$) is 3 weeks.

CONTRAINDICATIONS/WARNINGS

Use of tralokinumab-ldrm is contraindicated in patients with known hypersensitivity to tralokinumab-ldrm or any of its components; hypersensitivity reactions, including anaphylaxis and angioedema, have occurred after use tralokinumab-ldrm.

Conjunctivitis and keratitis occurred at an increased incidence in clinical trials in patients receiving tralokinumab-ldrm compared to patients receiving placebo. Advise patients to report any new or worsening eye symptoms to their healthcare provider.

Treat patients with helminth infections prior to initiation of tralokinumab-ldrm. If helminth infection occurs during tralokinumab-ldrm treatment and patient does not respond to antihelminth therapy, tralokinumab-ldrm should be discontinued until the infection resolves.

Use of live vaccines should be avoided during treatment with tralokinumab-ldrm due to the potential for altered immune response and increased risk of infection.

DRUG INTERACTIONS

Drug interactions studies were not performed with tralokinumab-ldrm.

COMMON ADVERSE EFFECTS

The most common adverse effects (≥ 1%) reported with tralokinumab-ldrm monotherapy relative to placebo, respectively, in monotherapy clinical trials, were upper respiratory tract infections (23.8% versus 20.4%), conjunctivitis (7.5% versus 3.1%), injection site reactions (7.4% versus 4.1%), and eosinophilia (1.4% versus 0.5%).

SPECIAL POPULATIONS

Pregnancy

Data for tralokinumab-ldrm in pregnancy are inadequate to advise of maternal or fetal risk. However, no maternal or embryofetal toxicity was observed in animal (monkey) studies.

Pediatrics

Safety and efficacy of tralokinumab-ldrm have not been established in pediatric patients (≤ 18 years of age).

Geriatrics

Clinical trials did not include an adequate number of patients ≥ 65 years of age to inform of differences in the safety and efficacy of tralokinumab-ldrm in this population compared to younger patients.

Hepatic Impairment

No clinically significant differences in the pharmacokinetics of tralokinumab-ldrm were observed in patients with mild hepatic impairment. The effect of moderate to severe hepatic impairment on the pharmacokinetics of tralokinumab-ldrm is unknown.

Renal Impairment

No clinically significant differences in the pharmacokinetics of tralokinumab-ldrm were observed in patients with mild to moderate renal impairment. The effect of severe renal impairment on the pharmacokinetics of tralokinumab-ldrm is unknown.

DOSAGES

Initial dose of 600 mg (4 x 150 mg subcutaneous [SC] injections), followed by 300 mg (2 x 150 mg SC injections) administered every other week.

After 16 weeks of treatment, in patients weighing < 100 kg who achieve clear or almost clear skin, a dosage of 300 mg (2 x 150 mg SC injection) every 4 weeks may be considered.

Tralokinumab-ldrm may be self-administered after proper training.

CLINICAL TRIALS[2,3,4]

A literature search was performed using "tralokinumab, ECZTRA 1, ECZTRA 2, and ECZTRA 3" and "atopic dermatitis."

The safety and efficacy of tralokinumab was assessed in three controlled trials, ECZTRA 1 (n=802), ECZTRA 2 (n=794), and ECZTRA 3. ECZTRA 1 and ECZTRA 2 were identically designed 52-week, randomized, double-blind, placebo-controlled, phase 3 trials that evaluated tralokinumab monotherapy in adult patients with moderate-to-severe AD with an inadequate response to topical treatments. Eligible patients were randomized 3:1 to SC tralokinumab 600 mg loading dose followed by 300 mg every other week or placebo for 16 weeks. The primary endpoints were Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at week 16 and ≥ 75% improvement in Eczema Area and Severity Index (EASI 75) at week 16. After the initial treatment period, tralokinumab-treated patients who achieved an IGA score of 0 or 1, or EASI 75 were rerandomized 2:2:1 to tralokinumab 300 mg every 2 weeks, tralokinumab 300 mg every 4 weeks, or placebo for maintenance for the duration of the study. Maintenance endpoints were maintenance of IGA score of 0 or 1 and EASI 75 at week 52. At 16 weeks, the primary endpoints occurred at a higher rate in the tralokinumab-treated patients compared to the placebo, respectively. In ECZTRA 1, IGA 0 or 1 was achieved by 15.8% versus 7.1% (difference 8.6%, 95% confidence interval (CI), 4.1 to 13.1; p=0.002) and in ECZTRA 2, by 22.2% versus 10.9% (difference 11.1%, 95% CI, 5.8 to 16.4; p<0.001). In ECZTRA 1, EASI 75 was achieved by 25% versus 12.7% (difference 12.1%, 95% CI, 6.5 to 17.7; p<0.001) and in ECZTRA 2, by 33.2% versus 11.4% (difference 21.6%, 95% CI, 15.8 to 27.3; p<0.001). At week 52, a majority of tralokinumab 16-week responders maintained clinical response with continued tralokinumab treatment without any rescue medication (including topical corticosteroids [TCS]). In ECZTRA 1 and ECZTRA 2, 51% and 59%, respectively, of patients who continued tralokinumab every other week, and 39% and 45% of those who changed to tralokinumab every 4 weeks maintained IGA response at 52 weeks without any use of rescue medication. In addition, 47% and 25% who switched from every other week tralokinumab to placebo maintained IGA response without rescue medication at week 52 in ECZTRA 1 and ECZTRA 2, respectively. Likewise, in ECZTRA 1 and ECZTRA 2, 60% and 56%, respectively, of patients who continued tralokinumab every other week, and 49% and 51% of those who changed to tralokinumab every 4 weeks maintained EASI 75 response at 52 weeks without any use of rescue medication, compared to 33% and 21% who switched from every other week tralokinumab.

ECZTRA 3 was a 32-week double-blind, placebo-controlled phase 3 trial that evaluated tralokinumab in combination with TCS in adult patients with moderate-to-severe AD who were candidates for systemic therapy. Eligible patients were randomized 2:1 to SC tralokinumab 600 mg loading dose followed by 300 mg every other week or placebo for 16 weeks. Patients in both groups received TCS as needed, once daily. The primary endpoints were IGA score of 0 or 1 at week 16 and EASI 75 at week 16. After the initial treatment period, tralokinumab-treated patients who achieved an IGA score of 0 or 1, or EASI 75 on tralokinumab were rerandomized 1:1 to tralokinumab 300 mg every 2 weeks or tralokinumab 300 mg every 4 weeks for maintenance for the duration of the study. Patients who achieved an IGA score of 0 or 1, or EASI 75 with placebo continued to receive placebo. Maintenance endpoints were maintenance of IGA score of 0 or 1 and EASI 75 at week 32. At 16 weeks, the primary endpoints occurred at a higher rate in the tralokinumab-treated patients compared to the placebo, respectively. At week 16, IGA 0 or 1

was achieved by 38.9% versus 26.2% (difference 12.4%, 95% CI, 2.9 to 21.9; p=0.015) and EASI 75 was achieved by 56% versus 35.7% (difference 20.2%, 95% CI, 9.8 to 30.6; p<0.001). At week 32, among the 16-week responders, an IGA response of 0 or 1 was maintained without rescue therapy (topical and systemic medications) with tralokinumab every 2 weeks and every 4 weeks in 89.6% (95% CI, 77.8 to 95.5) and 77.6% (95% CI, 64.1 to 87), respectively, and EASI 75 was maintained in 92.5% (95% CI, 83.7 to 96.8) and 90.5% (95% CI, 81.3 to 95.7), respectively.

OTHER DRUGS USED FOR CONDITION[5,6]

Emollients, topical corticosteroids, topical calcineurin inhibitors, crisaborole (Eucrisa®), ruxolitinib (Opzelura™) are topical agents indicated for the treatment of mild to moderate AD. Dupilumab (Dupixent®), upadacitinib (Rinvoq®), and abrocitinib (Cibnqo®) are systemic immunomodulators indicated for the treatment of moderate to severe AD.

PLACE IN THERAPY[7,8]

The 2014 American Academy of Dermatology (AAD) guidelines state that emollients, topical corticosteroids, and topical calcineurin inhibitors are the recommended agents for the treatment of atopic dermatitis (AD). For patients whose AD is not controlled by topical corticosteroids, or when there is a serious risk of adverse events from topical corticosteroids, topical calcineurin inhibitors (pimecrolimus and tacrolimus) are recommended. Although topical corticosteroids are the standard of care in the treatment of AD, dermatologic effects, such as striae, atrophy, and tachyphylaxis may limit their use. In addition, systemic absorption of topical steroids can result in systemic side effects, particularly with high- and very high–potency agents or prolonged continuous use. Concerns regarding linear growth rate, bone density, and hypothalamic-pituitary-adrenal (HPA) axis suppression may also limit the long-term use of these agents. Systemic immunomodulating agents are indicated for patients whose AD is not adequately controlled by topical regimens and/or phototherapy.

Tralokinumab-ldrm (Adbry) is an interleukin-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Like other systemic immunomodulating agents, tralokinumab-ldrm is indicated only when AD is not adequately controlled with topical therapies. Clinical trials demonstrate the efficacy of tralokinumab-ldrm for the treatment of moderate to severe AD as both monotherapy and in combination with topical corticosteroids. Dupilumab (Dupixent) is indicated for patients ≥ 6 years of age, while tralokinumab-ldrm is indicated only for use in adults. Upadacitinib (Rinvoq) and abrocitinib (Cibinqo) are both oral Janus kinase inhibitors (JAK) that received FDA-approval for the treatment of moderate-to-severe AD in January 2022, with the limitation that these agents should be used when AD is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable. In addition, all JAK inhibitors carry boxed warnings regarding the risks of serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis. Tralokinumab-ldrm was generally well tolerated in clinical trials. Overall, tralokinumab-ldrm provides an additional systemic self-administered injectable treatment option for adults with moderate to severe AD whose disease is not adequately controlled with topical therapy.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Immunomodulators, Atopic Dermatitis
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 18 years old; **AND** ▪ Patient will not receive live vaccines during therapy; **AND** ▪ Patient has a diagnosis of moderate to severe atopic dermatitis with at least 1 of the following: – Involvement of at least 10% of body surface area (BSA); **OR** – Eczema Area and Severity Index (EASI) score of 16 or greater; **OR** – Investigator's Global Assessment (IGA) score of 3 or more; **OR** – Scoring Atopic Dermatitis (SCORAD) score of 25 or more; **OR** – Incapacitation due to AD lesion location (i.e., head and neck, palms, soles, or genitalia); **AND** ▪ Patient has had a trial and failure, contraindication, or intolerance to at least 1 agent from ≥ 2 of the following classes: – Prescription topical corticosteroids – Topical calcineurin inhibitor (e.g., pimecrolimus or tacrolimus) – Topical phosphodiesterase-4 inhibitor (e.g., crisaborole) – Topical Janus kinase inhibitor (e.g., ruxolitinib); **AND** ▪ Tralokinumab-ldrm will not be used in combination with other monoclonal antibody biologics (e.g., tezepelumab, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab). **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Patient must have disease improvement and/or stabilization from baseline; **AND** ▪ Patient has NOT experienced serious treatment-related adverse events (e.g., serious infection, conjunctivitis, keratitis, eosinophilia).
Quantity Limit	4 syringes per 28 days
Duration of Approval	Initial: 16 weeks Renewal: 6 months
Drug to Disease Hard Edit	None

REFERENCES

1 Adbry [package insert]. Madison, NJ; Leo Pharma; December 2021.
2 Adbry [package insert]. Madison, NJ; Leo Pharma; December 2021.
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4 Silverberg JI, Toth D, Bieber T, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2021; 184(3): 450–463. DOI: 10.1111/bjd.19573
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6 Eichenfield L, Tom W, Chamlin S, et al. Guidelines of care for the management of atopic dermatitis. Available at: https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis. Accessed January 26, 2022.
7 Eichenfield L, Tom W, Chamlin S, et al. Guidelines of care for the management of atopic dermatitis. Available at: https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis. Accessed January 26, 2022.
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