CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761306Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761306
PDUFA Goal Date	September 28, 2023
NEXUS TTT #	2022-1989
Reviewer Name(s)	Leah Hart, PharmD
Acting Team Leader	Tim Bernheimer, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	September 21, 2023
Subject	Evaluation of Need for a REMS
Established Name	Lebrikizumab
Trade Name	Ebglyss
Name of Applicant	Eli Lilly and Company
Therapeutic Class	Interleukin-13 antagonist
Formulation(s)	Subcutaneous injection
Dosing Regimen	500 mg (two 250 mg injections) at week 0 and week 2, followed by 250 mg every 2 weeks (b) (4) week 16 or later; maintenance dose is 250 mg every 4 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ebglyss (lebrikizumab) is necessary to ensure the benefits outweigh its risks. Eli Lilly submitted a Biologic Licensing Application (BLA) 761306 for Ebglyss, is a subcutaneous (SC) injection, with the proposed indication of treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. There were no treatment deaths in the clinical trials. The risks associated with Ebglyss are hypersensitivity, conjunctivitis, and keratitis, parasitic (Helminth) infections, and risk of infection with live vaccines. The applicant did not submit a proposed REMS or risk management plan with this application.

The statistical reviewer has determined that Ebglyss showed benefit for the treatment of atopic dermatitis. The clinical reviewer is recommending approval at this time based on a favorable safety profile.

If approved, DRM has determined that a REMS is not needed to ensure the benefits of Ebglyss outweigh its risks. Other treatments, including oral corticosteroids and off-label immunosuppressants have a similar risk of infections; therefore, prescribers should be familiar with the risk and the steps to manage the risk. Prescribers are likely to be familiar and should have experience with the risks associated with Ebglyss, as they are well documented with the other approved IL antagonists (dupilumab and tralokinumab) used to treat AD, neither of these products are approved with a REMS. The Prescribing Information will include details on each risk with how to manage the risk.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ebglyss (lebrikizumab) is necessary to ensure the benefits outweigh its risks. Eli Lilly submitted a Biologic Licensing Application (BLA) 761306 for Ebglyss with the proposed indication of treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. This application is under review in the Division of Dermatology and Dentistry. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Ebglyss, a New Molecular Entity (NME) [a], is an immunoglobulin G4-related (IgG4) monoclonal antibody that binds to interleukin (IL)-13 and selectively inhibits IL-13 signaling through the IL4 receptor alpha/IL-13 receptor alpha-1 pathway, thereby blocking the downstream effects of IL-13 with high potency. IL-13 is a pleiotropic T helper type 2 (Th2) cytokine that is likely to play a role in the pathogenesis of barrier dysfunction and inflammation in atopic dermatitis.[1] The Applicant has proposed Ebglyss for the treatment of adults an adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topic prescription therapies or when those therapies are not advisable. Ebglyss is proposed to be administered by subcutaneous (SC) injection, with or without topical corticosteroids. The recommended dosage of Ebglyss is 500 mg (two 250 mg injections) at week 0 and week 2, followed by 250 mg every 2 weeks (b) (4) week 16 or later, when adequate clinical response is achieved. The maintenance dose is 250 mg every 4 weeks (b) (4) [b] If approved, Ebglyss would be a chronically administered medication.

Ebglyss is proposed as a prefilled pen (250 mg/2-mL) and prefilled syringe (250 mg/2-mL) by subcutaneous injection and will be used outpatient. Ebglyss is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for Ebglyss (BLA 761306) relevant to this review:

- 12/06/2019: Fast track designation granted
- 09/28/2022: BLA 761306 submission for the treatment of adult and adolescent patients 12 years of age and older with moderate-to-severe atopic dermatitis received
- 03/06/2023: A Post Mid-cycle communication meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Ebglyss.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease and often associated with an elevated serum level of immunoglobulin E (IgE).[2] Clinical features of AD include skin dryness, erythema, oozing and crusting, and lichenification.[3] Patients with AD have an increased risk of bacterial skin infections. *Staphylococcus aureus* is the most common organism to cause infection in AD.[4]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

In most cases, AD has an onset before the age of five years.[5] AD affects approximately 5 to over 20% of children worldwide.[6] The prevalence of AD among children worldwide is 15-20%.[7] [c,8] In the United States, a cross sectional study that included 1,278 participating adults found the prevalence (95% confidence interval) of AD was 7.3% (5.9-8.8).[9]

Several cohort studies and meta-analyses have found an association between atopic dermatitis and anxiety disorder, depression, suicidal ideation, and attempted suicide in adults and children. [d,10,11] AD can cause an increase in sleep disturbances in children due to discomfort and scratching at night.[12] In one study, AD was found to be equivalent in family impact to other non-dermatologic chronic childhood disorders using the Children's Life Quality Index.[13] AD had the second highest score following cerebral palsy. Adults with AD reported higher proportions of having only fair/poor overall health (25.8% vs. 15.8%) and being somewhat/very dissatisfied with life (16.7% vs 11.4%).[14] This study also found that AD is commonly limited lifestyle (51.3%), led to avoidance of social interaction (39.1%), and impacted activities (43.3%). The most burdensome AD symptoms were itch (54.4%), excessive dryness/scaling (19.6%), and red/inflamed skin (7.2%).

3.2. Description of Current Treatment Options

Treatment for AD falls into several pharmaceutical categories including topical treatments (corticosteroid, calcineurin inhibitor, phosphodiesterase 4 (PDE4) inhibitor, Janus kinase (JAK) inhibitor) and systemic treatments (interleukin (IL) 4/IL-13 receptor antagonist, monoclonal anti-IL-13 antibody, and JAK inhibitor). FDA approved treatments for atopic dermatitis other than corticosteroids are listed in Appendix 1

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups.[10] Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. Long term use of TCS may lead to systemic absorption and systemic adverse events including adrenal suppression, osteoporosis, and type 2 diabetes.[15,16] Local effects can include skin thinning, atrophy, telangiectasia, and striae.[17] Various oral corticosteroids are approved for use in atopic dermatitis and used for acute exacerbations. These steroids carry Warnings and Precautions that include alterations in endocrine function, increased risks related to infections, alterations in cardiovascular/renal functions, increased risk of GI perforation, behavioral and mood disturbances, risk of infection with live vaccinations, among others.[18] Other non-approved therapies include cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, and omalizumab, all of which have an increased susceptibility to infection due to their immunosuppression; therefore, prescribers familiar with these therapies should be knowledgeable about the risk of infection with AD treatment.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Over the counter treatment includes topical steroids, topical diphenhydramine, topical antipruritic ingredients such as phenol, menthol, and camphor and sedating and non-sedating oral antihistamines. Non-pharmacological therapies include the elimination of exacerbating factors (allergens, etc.), and maintaining skin hydration through emollients, moisturizers, proper bathing practices, colloidal oatmeal creams and soaks and phototherapy.

The Applicant has stated that there is an unmet medical need; that, while several therapies are currently available to patients with moderate-to-severe AD, they are associated with limitations to long term use and variable response rates.

4. Benefit Assessment

Two adequate and well-controlled pivotal trials, ADvocate 1 (KGAB) and ADvocate 2 (KGAC) and one supportive trial, ADhere (KGAD) support this application. These trials were randomized, double-blind, placebo-controlled trials in subjects 12 years of age and older with moderate-to-severe atopic dermatitis not adequately controlled by topical medication(s) or when those therapies were not advisable. KGAB and KGAC evaluated lebrikizumab as monotherapy, and KGAD evaluated lebrikizumab with protocol-specified, concomitant use of TCS.

All three trials assessed the primary endpoint, the percentage of responders to the treatment, defined as an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline at Week 16. Other evaluated outcomes at Week 16 included the proportion of subjects with at least 75% reduction in Eczema Area and Severity Index (EASI) (EASI-75) from baseline and not receiving any rescue treatment during the 16-week induction period. Several disease severity scales exist including the Eczema Area and Severity Index [EASI] which is used to measure the extent (area) and severity of AD. The score ranges from 0 (no active eczema) to 6 (90-100% of the region is affected by eczema.[19]In all three trials, subjects in the lebrikizumab group received subcutaneous injections of lebrikizumab 500 mg at Week 0 and at Week 2, followed by 250 mg every other week (Q2W) through Week 16. After completing the Week 16 visit, participants who responded to the lebrikizumab treatment were randomly reassigned in a 2:2:1 ratio to one of the following groups: lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo Q2W. Participants who did not achieve an IGA score of 0 or 1 nor an EASI 75 at Week 16 or who received topical or systemic rescue therapy between baseline to Week 16 were assigned to an Escape Arm and received open-label lebrikizumab 250 mg Q2W through Week 52.

KGAB randomized 424 subjects, 283 to lebrikizumab and 141 to placebo. KGAC randomized 445 subjects, 295 to lebrikizumab and 150 to placebo; 18 subjects were excluded due to a critical finding at a site audit. KGAD randomized 228 subjects, 153 to lebrikizumab + TCS and 75 to placebo + TCS; 17 subjects were excluded due to a critical finding at the site audit. Eighteen participants in KGAC, and 17 from KGAD were excluded due to protocol deviations, resulting in 146 patients in the placebo group and 281 in the treatment group for KGAC and 66 patients in the placebo group + TCS and 145 patients in the treatment + TCS group for KGAD.

The primary endpoint of percentage of participants achieving IGA 0 or 1 and a 2-point or greater improvement from baseline at Week 16 of induction period was met. A significantly greater percentage of participants achieved IGA 0 or 1, with a 2-point or more reduction at Week 16 in the lebrikizumab-treated group compared with the placebo-treated group in KGAB and KGAC; KGAD is not statistically significant.

The following are the results of each study for the primary endpoint

ADvocate1: placebo-treated group, 12.7%; lebrikizumab-treated group, 43.1%; p<0.001
Advocate 2: placebo-treated group, 10.8%; lebrikizumab-treated group, 33.2%; p<0.001
ADhere: placebo-treated group, 22.1%; lebrikizumab-treated group, 41.2%; p=0.011

The key secondary endpoints are EASI-75 (≥75% reduction from baseline), EASI-90 (≥90% reduction from baseline) and pruritus NRS (numerical rating scale) score (i.e., at least a 4-point reduction from baseline in Worst Daily Pruritus NRS score) at week 16 in the monotherapy trials. Lebrikizumab was statistically superior to placebo for EASI-75, EASI-90, and pruritus NRS score at week 16.

The clinical reviewer concludes that the Applicant has provided substantial evidence of effectiveness from 2 adequate and well-controlled trials and 1 supportive trial. Lebrikizumab was statistically superior to placebo in Studies KGAB and KGAC in the target AD population for the primary endpoint of IGA success (defined as scoring 0 or 1 with ≥2-point reduction from baseline) and EASI-75 (≥75% reduction from baseline) at week 16.[20,e]

5. Risk Assessment & Safe-Use Conditions

The safety of lebrikizumab was evaluated 1756 subject including 382 adolescents across 8 clinical studies.[21] A total of 903 subjects were treated with lebrikizumab for at least 1 year in the atopic dermatitis development program; of those, 272 were adolescents. A total of 754 subjects were exposed to lebrikizumab 250 mg Q2 weeks as the only treatment for at least 1 year; 247 were adolescents. The primary focus of the safety review is on the data from ADvocate 1, ADvocate 2, and ADhere.

There were four deaths in the development program for AD. The Applicant reported that none of these deaths were assessed as related to lebrikizumab. One subject experienced a fatal heart attack on study day 8, one had pancreatic carcinoma with metastases to the liver and bone and died in hospice on study day 337, one died of what was considered to be natural causes on study day 462, a 13-year-old subject experienced a cardiac arrest on study day 155 attributed to COVID-19, and a subject with pancreatic cancer with metastases to the liver. The clinical reviewer agrees with the assessment that the five deaths do not appear to be related to the drug.[20]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Serious adverse events experienced during the induction period were similar in frequency between lebrikizumab and placebo groups as well as during the monotherapy maintenance period.[f] The clinical reviewer agreed with the assessment of the investigators that the SAEs were not related to study drug.[20] The most common AE leading to drug discontinuation was conjunctivitis in the lebrikizumab-treated groups.

5.1. Hypersensitivity Reactions

The frequency of hypersensitivity reactions was low in both the placebo and the lebrikizumab-treated subjects in the induction and maintenance periods. Across all lebrikizumab exposure, hypersensitivity occurred in 1.5% of subjects receiving lebrikizumab with urticaria occurring in 0.9% of subjects. No events of anaphylaxis or angioedema were reported but there were events of drug eruption that occurred. Based on the events seen in the clinical development program, and the fact that angioedema and anaphylaxis have occurred after administration of other IL-13 antagonists (tralokinumab), hypersensitivity will be included in Warnings and Precautions with instructions to discontinue Ebglyss and institute appropriate therapy.[22]

5.2. Conjunctivitis and Keratitis

Conjunctivitis was an AESI due to the potential association with the mechanism of action of lebrikizumab, the AEs observed for other drugs in the same class, and the increased incidence of conjunctivitis in AD patients.[g] Ocular events, including conjunctivitis, blepharitis, and keratitis were reported more frequently in the lebrikizumab group compared to placebo. During the placebo-controlled induction period (Weeks 0 to 16), conjunctivitis was reported in 6.3% of subjects compared to 1.7% of placebo subjects (95% CI -7.14, -2.26). During the placebo-controlled maintenance period (Weeks 16 to 52), the frequency of ocular events was similar in the Q4 week group compared to placebo (7.5% and 3.2% respectively) and lower in the Q2 week group compared to placebo (1.7% and 3.2% respectively). The risk of keratitis was similar between placebo and lebrikizumab.

The risk of conjunctivitis and keratitis will be included in the Warnings and Precautions section of the label. As with other interleukin antagonists, healthcare providers are instructed to advise patients to report new onset or worsening eye symptoms to their healthcare provider.[22]

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[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.3. Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies and there were no events of parasitic infections reported for the lebrikizumab and placebo groups in any of the placebo-controlled induction period or maintenance period. The prescribing information will include the risk of parasitic (helminth) infections in the Warnings and Precautions section, similar to other drugs in the same class. Healthcare providers are instructed to discontinue treatment with Ebglyss if a patient becomes infected while receiving Ebglyss and are not responding to antihelminth treatment until the infection resolves.[22]

5.4. Risk of Infection with Live Vaccines

Although the risk of immunizations with live vaccines was not identified in the clinical development program, this is a class risk and will be included in Warnings and Precautions. The label instructs providers to consider completion of all age-appropriate immunizations according to current immunization guidelines but to avoid the use of live vaccines. There is no data on the response to live (b) (4) vaccines.[22]

6. Expected Postmarket Use

Ebglyss is expected to be used in the outpatient setting as chronic therapy and will be self-administered by the patient or caregiver.

Dermatologists, allergists, primary care providers and pediatricians are likely to prescribe the drug are familiar with the risks of hypersensitivity, conjunctivitis and keratitis, parasitic (Helminth) infections, and risk of infection with live vaccines because the other IL-13 antagonist approved for AD carries the same risks. In addition, oral corticosteroids, and off label immunosuppressants carry similar risks of infections; therefore, prescribers should be aware of the risks associated with the treatment of AD. The likely prescribers should have the necessary knowledge to manage the risk by counseling patients on the risks and how to manage those risks including avoiding live vaccines in patients using Ebglyss. The likely patient population are adult and adolescent patients 12 years of age and older. Pediatric patients will have a caregiver to make medical decisions on their behalf.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for lebrikizumab beyond routine pharmacovigilance and labeling. The Applicant stated that, “based on current information from the ongoing evaluation of the clinical safety of lebrikizumab, and as summarized in the application, Lilly believes that labeling will adequately communicate safety risks to prescribers.”

Post Marketing Requirements

At the time of this review, the review team has made a preliminary evaluation of anticipated post marketing requirements (PMRs), which includes:

- Conducting or participating in a relevant Pregnancy Exposure Registry designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes.
- An additional pregnancy study that uses a different design that the Pregnancy Exposure Registry to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age and preterm birth in women exposed to lebrikizumab during pregnancy

Reviewer's Comments: *We note that these studies could provide additional information about safety; however, this reviewer defers to Divisions of Pharmacovigilance and Epidemiology for review and input on the proposed post marketing requirement studies.*

8. Discussion of Need for a REMS

Lebrikizumab is an interleukin-13 antagonist proposed for the treatment of adult and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The two pivotal trials, ADvocate 1, ADvocate 2, and the supportive trial ADhere, support the efficacy of lebrikizumab as evidenced by a statistically significant improvement in IGA score, EASI-75, EASI-90, and pruritus NRS score, with an acceptable safety profile and the clinical reviewer recommends approval of Ebglyss based on the efficacy and safety information currently available.

The risks associated with use are hypersensitivity, conjunctivitis, and keratitis, parasitic (Helminth) infections, and risk of infections with live vaccines which are similar to the risks of other products used to treat AD, including IL-13 antagonist tralokinumab and IL antagonist dupilumab. Other treatments, including oral corticosteroids and off-label immunosuppressants have a similar risk of infections; therefore, prescribers should be familiar with the risk and the steps to manage the risk. The safety of lebrikizumab is similar to the other approved interleukin-13 antagonist, tralokinumab. Prescribers are likely to be familiar and should have experience with these risks as they are well documented with the other approved IL antagonists (dupilumab and tralokinumab) used to treat AD, neither of these products are approved with a REMS. In addition, these products are outlined in the 2023 American Academy of Allergy, Asthma & Immunology (AAAAI)/ American College of Allergy, Asthma and Immunology (ACAAI) Atopic Dermatitis (Eczema) Guidelines.[23] The guideline outlines the risks associated with the products, approved and unapproved, used to treat AD.

This reviewer has determined that a REMS is not necessary to ensure the benefits of lebrikizumab outweigh its risks. The risks will be included in the Warnings and Precautions section of the label with instructions in each section for managing the risk.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Ebglyss to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. Summary of Treatment Options Relevant to Atopic Dermatitis

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Safety/Tolerability	Risk Management
Topical Treatments				
Elidel (pimecrolimus)[24] 12/13/2001	Second line therapy for short-term and non-continuous chronic treatment of mild to moderate AD	Thin layer twice daily	Long-term use safety concerns	Boxed warning for long-term safety concerns with rare cases of malignancy; W&P no immunocompromised adults and children, no malignant or pre-malignant skin conditions
Protopic (tacrolimus)[25] 12/08/2000	Second line therapy for short-term and non-continuous chronic treatment of moderate to severe AD	Minimum amount twice daily	Long-term use safety concerns	Boxed warning for long-term safety concerns with rare cases of malignancy; W&P no immunocompromised adults and children, no safety established beyond one year of non-continuous use; Medication Guide (MG)
Eucrisa (crisaborole)[26]	Topical treatment of mild to moderate AD in adult and pediatric patients 3 months of age and older	Thin layer twice daily	Hypersensitivity	W&P for hypersensitivity
Zonalon (doxepin)[27]	Short-term (up to 8 days) management of moderate pruritus in adult patients with AD	Thin layer four times daily	Drowsiness	W&P for drowsiness
Opzelura (ruxolitinib)[28] 09/21/2021	Topical short-term and non-continuous treatment of mild to	Thin lawyer twice daily	Serious infections, mortality (higher all-cause),	Boxed warning; W&P; MG

	moderate AD in non-immunocompromised patients 12 years of age or older		malignancy, MACE, thrombosis	
Systemic Treatments				
Dupixent (dupilumab)[29] 03/28/2017	Treatment of adult and pediatric patients aged 6 months and older with moderate to severe AD	SubQ: Initial dose of 600 mg followed by 300 mg every other week; weight-based dosing for pediatric patients	Hypersensitivity, conjunctivitis and keratitis, eosinophilic conditions, acute asthma symptoms	W&P for 9 concerns; MG
Adbry (tralokinumab-ldrm)[30] 12/27/2021	Treatment of moderate-to severe AD in adult patients	SubQ Initial dose of 600 mg followed by 300 mg every other week	Hypersensitivity, conjunctivitis, parasitic infections, risk of infection with live vaccine	W&P, MG
Cibinqo (abrocitinib)[31] 1/14/2022	Treatment of adults with refractory, or moderate to severe AD	100 mg once daily; 200 mg once daily for those not responding to 100 mg	Serious infections, mortality (higher all-cause), malignancy, MACE, thrombosis	Boxed warning; W&P (lab abnormalities, immunizations); MG
Rinvoq (updacitinib)[32] 8/16/2019	Treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe AD	Pediatric patients 12 years of age and older weighing at least 40kg:15 mg once daily. Can increase to 30mg if no response. Adults 65 and older: 15 mg once daily	Serious infections, mortality (higher all-cause), malignancy, MACE and thrombosis	Boxed warning; W&P (serious infections, hypersensitivity, GI perforations, lab abnormalities, embryo-fetal toxicity, immunizations); MG

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