APRIL 2021

PERSPECTIVE ON THE Rx PIPELINE

Understanding changes in the medication market and their impact on cost and care.

elixir
CRAFTED Rx SOLUTIONS

Perspective on the Rx Pipeline

Elixir continuously monitors the drug pipeline. As treatment options change, we evaluate and share our perspective on the clinical benefits, cost-effectiveness and overall impact to payers and patients. Our Perspective on the Rx Pipeline report provides ongoing actionable insights from our team of clinical experts and the steps we are taking to protect and improve plan performance.

INCLUDED IN THIS EDITION:

Needed Relief for Hard-to-Treat Skin Condition:
New Treatment Options in the Drug Pipeline for Atopic Dermatitis

ATOPIC DERMATITIS

Needed Relief for Hard-to-Treat Skin Condition: New Treatment Options in the Drug Pipeline for Atopic Dermatitis

PIPELINE STAGE

TIMING

When will payers be impacted?

CLINICAL EFFECTIVENESS

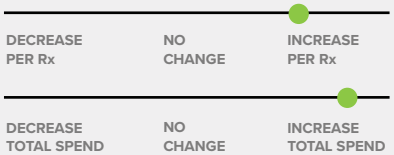
Compared to available options, is this drug better for treatment?

MEMBER EXPERIENCE

Will this positively or negatively impact members?

PAYER IMPACT

How will this influence Rx spend?



Situation Summary

Atopic dermatitis (AD) is a skin condition that affects approximately 9.6 million children in the United States, with an estimated 16.5 million continuing to suffer from the condition as adults.[1] While it is more prevalent in children, adult on-set of AD can also occur. AD may be viewed as just a rash, but it can have a profound effect on a person's quality of life. In a recent study, 70.5% of participants with AD reported severe, unbearable itching that can impact sleep and other daily activities.[1] As the pipeline of prescription options to help treat this chronic condition continues to expand, it could also have an impact on healthcare costs.

AD is a chronic condition that can flare up with environmental factors, triggers or other comorbidities (e.g., eczema, asthma, food allergies or allergic rhinitis).[2] It can vary in severity and presentation, such as irritated skin patches that are swollen and itchy. Over time, there can be skin thickening or fissuring in areas of chronic scratching, and some patches can be at risk for viral or bacterial infections.[3] Diagnosis is based on history and skin lesion evaluation. Some data has shown that earlier age of onset could determine severity and longevity into adulthood.[4]

Treatment Options: While there are a variety of both pharmacological and non-pharmacological treatment options for AD, moderate to severe forms of the condition are often resistant to therapy.

Perfumes, dyes and other ingredients in a daily skin care routine can trigger AD, so the most standard non-pharmacological approach of doctors is to teach good skin care habits (e.g., application of moisturizer, warm bath or a shower using non-soap cleanser) and trigger avoidance, including removal of scented detergents or soaps. Adding in antibiotics and even antiseptics may become necessary as the number of patches and symptoms increase or worsen.[2]

Unfortunately, sometimes avoidance and over-the-counter options are not enough and many AD sufferers have to start using prescription treatments to get their condition under control. First-line prescription treatments include topical corticosteroids, starting with low-medium potency, followed by topical calcinuerin inhibitors (TCI) or Eucrisa® (crisaborole). As the condition worsens or if it is considered severe, treatment can include phototherapy, Dupixent® (dupilumab), the first biologic approved for the treatment of AD, or systemic immunosupressants (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine or oral corticosteroids). [2, 5] Systemic immunosupressants can have side effects or be difficult to tolerate.

ATOPIC DERMATITIS

Continued from previous page

Current Prescription Therapy Options for Atopic Dermatitis[6, 7]

Drug Class	Example Medications	AD Severity Initiation	Clinical Notes
Topical corticosteroids	Low potency corticosteroid cream or ointment (desonide 0.05%, hydrocortisone 2.5%)	Mild-severe	• First-line therapy • Low potency for mild disease • Medium to high potency for moderate disease • For acute flares, high-potency steroids can be used for up to 2 weeks and transitioned back to lower potency
Topical calcinuerin inhibitors	• Pimecrolimus 1% cream • Tacrolimus 0.03 to 0.1 % ointment	Mild-moderate	• Approved for use in children > 2 years of age • Second-line therapy • Works similar to corticosteroids, however, does not cause thinning of the skin • Safety concerns remain with this class; use as second-line therapy in patients unresponsive to first-line treatment • Application should be limited to flared areas for shortest duration of therapy • Tacrolimus can cause burning and stinging
Topical phosphodiesterase (PDE) 4 inhibitor[8]	Eucrisa (crisaborole)	Mild-moderate	• Approved in patients > 3 months • Reduces pruritus (itching)
Systemic immunosuppressants	• cyclosporine • methotrexate • mycophenolate mofetil • azathioprine • oral corticosteroids	Severe	• Products do not have FDA-approved labeling for AD and are off-label use, except for the oral corticosteroid prednisolone • Products do not target specific point in immune dysregulation of AD, so can have systemic side effects (kidney/liver dysfunction) • Limited to cases that have not shown effective response to topical therapy, may be some hesitance to use in a pediatric population
IL-4 and IL-13 Inhibition[9-10]	Dupixent (dupilumab)	Moderate-severe	• Approved for children 6 years of age and older • Combination therapy with topical steroids has been more effective than Dupixent alone

ATOPIC DERMATITIS

Continued from previous page

PRIMARY ENDPOINT DEFINITIONS

- **Investigator Global Assessment (IGA) response**
  Clear (0) or almost clear (1)
- **Eczema Area and Severity Index score (EASI-75)**
  The proportion of participants achieving at least 75% improvement at week 12
- **Visual-Analogue Scale (VAS) score for pruritus**
  Range of 0 to 100, with higher scores indicating worse pruritus

Atopic Dermatitis Treatment Options in the Pipeline: Atopic dermatitis is associated with an immune system response. It primarily involves interleukin (IL) cytokines, which are secreted by immune cells and may be inflammatory. Specifically, janus kinase (JAK) activation may be involved in signaling more than 50 cytokines, including IL-4, IL-5, IL-13 and IL-31 . Many of the medications in the development pipeline for the treatment of AD utilize a mechanism of action that targets these cytokines and JAK enzymes.[11, 12]

There are already approved JAK inhibitors on the market for the treatment of other diseases, such as rheumatoid arthritis, graft-versus-host disease, myelofibrosis and ulcerative colitis. It is hypothesized that JAK inhibition not only modifies the body's immune response, but possibly improves the skin as well. JAK inhibitors are not biologics; they are disease-modifying agents approved through the FDA new drug application (NDA) process. Recently, JAK inhibitors' benefit-risk profile has been under scrutiny, including their long-term safety profile, which could determine much of the upcoming FDA reviews for these pipeline AD oral products.

Tralokinumab and lebrikizumab are drugs in the pipeline that selectively target IL-13 inhibition, similar to Dupixent. The first IL-31 inhibitor, nemolizumab, is also in the pipeline. IL-31 is known as the "itch cytokine." Nemolizumab blocks IL-31 signaling on effector cells and in peripheral neurons.[6]

Atopic Dermatitis Pipeline Comparison[11, 13-18]

Drug	Route	Mechanism of Action	Primary/ Co-Primary Endpoint	Anticipated FDA Decision Date	Clinical Notes
abrocitinib	Oral	JAK1	IGA with improvement of ≥2 grades and EASI-75 *(see sidebar above for definitions)*	3Q2021	• Indicated for patients 12 years of age and older • FDA extended the review time needed

Clinical Studies for abrocitinib

Phase III – An IGA score of 0 or 1 was achieved in 59 out of 155 participants taking the 200 mg dose (38.1%) and 44 out of 155 participants taking the 100 mg dose (28.4%) vs 7 out of 77 (9.1%) participants taking the placebo; $P < 0.001$

EASI-75 was achieved in 94 out of 154 participants taking the 200 mg dose (61.0%) and 69 out of 155 participants taking the 100 mg dose (44.5%) vs 8 out of 77 participants taking the placebo (10.4%); $P < 0.001$.

Serious adverse events were reported for 2 participants (1.3%) in the 200 mg group, 5 (3.2%) in the 100 mg group and 1 (1.3%) in the placebo group.

Limitations include a relatively small population under 18 years of age or over 65 years of age, a limited African American population, and duration of treatment was short.

ATOPIC DERMATITIS

Continued from previous page

Drug	Route	Mechanism of Action	Primary/ Co-Primary Endpoint	Anticipated FDA Decision Date	Clinical Notes
Olumiant (baricitinib)	Oral	JAK1/2	IGA	1H2021	• Indicated for adults only • Approval granted in European Union • Olumiant is currently FDA approved for rheumatoid arthritis and has a boxed warning for serious infections, malignancies and thrombosis
Clinical Studies for Olumiant Phase III (BREEZE-AD3) – 45.7% of responders taking the 4 mg dose achieved an IGA score of 1 or 0, while 40% maintained response over 68 weeks of therapy 46.3% of responders taking 2 mg achieved an IGA score of 1 or 0, while 50% maintained response after 68 weeks of therapy					
Rinvoq (upadacitinib)	Oral	JAK1	EASI-75 at week 16	8/2021	• Indicated for patients 12 years of age and older • FDA approved for rheumatoid arthritis • Head-to-head trial against Dupixent • FDA extended the review time requesting more information on safety of JAK inhibitor class
Clinical Studies for Rinvoq Phase III - 71% of participants treated with upadacitinib achieved an EASI-75, compared to 61% of participants treated with dupilumab at week 16; P = 0.006					
ruxolitinib (RUX)	Topical	Selective JAK1/2	Mean percent change of EASI at week 4	6/21/2021	• Indicated for patients 12 years of age and older • Priority review • Study population includes mild to moderate AD
Clinical Studies for ruxolitinib Phase II - 1.5% RUX cream twice daily demonstrated a significantly greater mean percentage change from baseline in EASI scores versus vehicle at week 4; 71.6% vs 15.5%; P < .0001					
tralokinumab	Subcutaneous injection	IL-13	IGA and ≥ EASI-75 at week 16	2Q2021	• Monoclonal antibody • Combination with topical corticosteroids • Indicated for adults only • Every 2 to 4 weeks dosing
Clinical Studies for tralokinumab Phase II – 15.8% of participants taking tralokinumab vs. 7.1% of those taking a placebo achieved the IGA score of 0 or 1 during the ECZTRA 1 trial; P = 0·002, and in the ECZTRA 2 trial, 22.2% of participants taking tralokinumab vs. 10.9% of participants taking a placebo achieved the IGA score of 0 or 1; P < 0·001 In ECZTRA 1, 25.0% of participants achieved EASI-75 vs. 12.7% of those taking a placebo; P < 0·001, and in ECZTRA 2, 33.2% of participants achieved EASI-75 vs. 11·4% of those taking a placebo; P < 0·001					

ATOPIC DERMATITIS

Continued from previous page

Drug	Route	Mechanism of Action	Primary/ Co-Primary Endpoint	Anticipated FDA Decision Date	Clinical Notes
lebrikizumab	Subcutaneous injection	IL-13	Percent change in EASI-75 (least squares mean) from baseline at week 16	Currently in Phase III	• Monoclonal antibody • Indicated for patients 12 years of age and older • Every 2 to 4 weeks dosing
Clinical Studies for lebrikizumab Phase II – Percent change ranged from -62.3% (125 mg every 4 weeks) to -69.2% (250 mg dose every 4 weeks) to 72.1% (250 mg every 2 weeks) vs placebo; the 250 mg every 2 weeks reached a P<0.001					
nemolizumab	Subcutaneous injection	IL-13	VAS from baseline to week 16	Currently in Phase III	• Monoclonal antibody • Inhibiting IL-31 significantly improved AD-associated pruritus • Combination with topical treatment • Indicated for patients 12 years of age and older • Every 4 weeks dosing
Clinical Studies for nemolizumab Phase III - At week 16, the mean percent change in the VAS score was −42.8% for the nemolizumab group vs −21.4% in the placebo group (difference, −21.5 percentage points; 95% confidence interval, −30.2 to −12.7; P<0.001) Severe adverse events occurred in 3 nemolizumab patients and were reported as meiniere's disease, acute pancreatitis and atopic dermatitis worsening. A limitation of the study was that it only included Japanese patients.					

ATOPIC DERMATITIS

Continued from previous page

PAYER ACTION PLAN

- **Monitor the Drug Pipeline**
  At this time, there is no action that payers need to take. Elixir will continue to monitor the AD drug pipeline and keep our clients apprised of updates. Our P&T committee will review any newly approved FDA products and update clients when these products may be available for member utilization.

Impact to the Pharmacy Care Experience

Pipeline Monitoring: Elixir is closely monitoring this drug pipeline, which mainly focuses on moderate to severe AD.

Pharmacy & Therapeutics Review and Formulary Strategies: Elixir's Pharmacy & Therapeutics (P&T) committee, which helps determine a drugs formulary placement, will rigorously review each future FDA approval to assure clinically appropriate, safe and efficacious products are provided on the formulary.

The safety profile of JAK inhibitors may be paramount in the FDA approval of any pipeline products for AD and will be something to review. Additionally, IL-13 inhibitors will want to prove comparable or superior to Dupixent's already established safety and efficacy, as well as potentially offer an easier administration (such as oral or less frequent dosing) and a better value profile. It may take some time before true competition drives market share away from Dupixent when moderate to severe AD requires an immune suppressant. IL-31 inhibitor, nemolizumab, may find its place for patients experiencing severe itching not resolvable by current treatments. Elixir will conduct a value assessment of current-market products after clinical review.

Utilization Management: Utilization management, such as prior authorization, may be needed on pipeline medications to ensure clinically appropriate, first-line treatments were tried and that AD severity is met.

Sources

[1] National Eczema Association. Eczema Stats. https://nationaleczema.org/research/eczema-facts/.

[2] Eichenfield, L. F., et al (2014). Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. Journal of the American Academy of Dermatology, 70(2), 338–351. https://doi.org/10.1016/j.jaad.2013.10.010

[3] Balma-Mena, A., et al. (2011). Colonization with community-acquired methicillin-resistant Staphylococcus aureus in children with atopic dermatitis: a cross-sectional study. International journal of dermatology, 50(6), 682–688. https://doi.org/10.1111/j.1365-4632.2010.04751.x

[4] Kim, J. P., Chao, L. X., Simpson, E. L., & Silverberg, J. I. (2016). Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. Journal of the American Academy of Dermatology, 75(4), 681–687.e11. https://doi.org/10.1016/j.jaad.2016.05.028

[5] Boguniewicz, M., et al. (2018). Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology, 120(1), 10–22.e2. https://doi.org/10.1016/j.anai.2017.10.039

[6] Ständer S. (2021). Atopic Dermatitis. The New England journal of medicine, 384(12), 1136–1143. https://doi.org/10.1056/NEJMra2023911

[7] Sidbury, R., et al. (2014). Guidelines of care for the managment of atopic dermatitis. Journal of the American Academy of Dermatology. https://doi.org/10.1016/j.jaad.2014.03.030.

[8] Eucrisa Ointment 2% (crisaborole) [prescribing information]. New York, NY: Pfizer Labs; April 2020.

[9] Tameez Ud Din, A., Malik, I., Arshad, D., & Tameez Ud Din, A. (2020). Dupilumab for Atopic Dermatitis: The Silver Bullet We Have Been Searching for?. Cureus, 12(4), e7565. https://doi.org/10.7759/cureus.7565

[10] Dupixent (dupilumab) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals; June 2020.

[11] Kim, B. S., et al. (2020). Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. The Journal of allergy and clinical immunology, 145(2), 572–582. https://doi.org/10.1016/j.jaci.2019.08.042

[12] Renert-Yuval, Y., & Guttman-Yassky, E. (2020). New treatments for atopic dermatitis targeting beyond IL-4/IL-13 cytokines. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology, 124(1), 28–35. https://doi.org/10.1016/j.anai.2019.10.005

[13] Silverberg, J. I., et al. (2020). Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA dermatology, 156(8), 863–873. https://doi.org/10.1001/jamadermatol.2020.1406

[14] EADV 2020: Lilly and Incyte Showcase New Data for Baricitinib for the Treatment of Moderate to Severe Atopic Dermatitis. Eli Lilly and Company (2020, October). Lilly Investors. Retrieved April 08, 2021, from https://investor.lilly.com/news-releases/news-release-details/eadv-2020-lilly-and-incyte-showcase-new-data-baricitinib

[15] RINVOQ™ (upadacitinib) Achieved Superiority Versus DUPIXENT® (dupilumab) For Primary and All Ranked Secondary Endpoints in Phase 3b Head-to-Head Study in Adults with Atopic Dermatitis. (2020 December). Abbvie News Center. Retrieved April 08, 2021 from https://news.abbvie.com/news/press-releases/rinvoq-upadacitinib-achieved-superiority-versus-dupixent-dupilumab-for-primary-and-all-ranked-secondary-endpoints-in-phase-3b-head-to-head-study-in-adults-with-atopic-dermatitis.htm

[16] Wollenberg, A., et al (2021). Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). The British journal of dermatology, 184(3), 437–449. https://doi.org/10.1111/bjd.19574

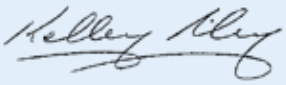
[17] Guttman-Yassky, E., et al. (2020). Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. JAMA dermatology, 156(4), 411–420. https://doi.org/10.1001/jamadermatol.2020.0079

[18] Kabashima, K., Matsumura, T., Komazaki, H., Kawashima, M., & Nemolizumab-JP01 Study Group (2020). Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. The New England journal of medicine, 383(2), 141–150. https://doi.org/10.1056/NEJMoa1917006

Our Clinical Steering Committee

The Elixir Clinical Steering Committee brings together leaders from across our national pharmacy care company to monitor the drug landscape, provide recommendations on how to address changes, and to ensure our clients and patients are prepared—in advance.

With any new development, we partner with our Pharmacy & Therapeutics (P&T) committee and consult with our best-in-class specialty pharmacy, to provide a balanced perspective on the clinical effectiveness of all available options, the cost impact to our plan sponsors and patients, and the impact on the overall patient experience.



Kel Riley, MD
Chief Medical Officer

More ways to improve member and plan outcomes

elixirsolutions.com

About Elixir | elixirsolutions.com

With the unique ability to optimize the full pharmacy care experience, Elixir is crafting solutions for today's pharmacy benefits challenges. For more information, visit elixirsolutions.com.

elixir
CRAFTED Rx SOLUTIONS