Drug Monograph

Drug Name: **Opzelura™ (ruxolitinib) cream**
Drug Class: **Janus Kinase Inhibitor**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Opzelura is available in a 60 g tube containing 1.5% ruxolitinib cream.
Manufacturer:	Distributed by: Incyte Corporation, Wilmington, DE 19803.
Summary of Findings:	The efficacy of Opzelura was demonstrated by two randomized, double-blind, vehicle-controlled, Phase 3 studies (TRuE AD1 and TRuE AD2). Study participants were adolescents and adults ≥12 years with mild to moderate atopic dermatitis. Patients were randomized to be treated with Opzelura or vehicle topically twice daily. Patients were evaluated with the Investigator's Global Assessment Treatment Success (IGA-TS) tool and the primary endpoint was the proportion of patients achieving IGA-TS, from baseline at Week 8. Data from the studies show that 53.8% and 51.3% of Opzelura-treated patients in the TRuE AD1 and TRuE AD2, respectively, met the primary endpoint at Week 8 versus 15.1% and 7.6% of vehicle-treated patients ($p<0.0001$). Like the oral Janus kinase inhibitors, Opzelura carries a black box warning for serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.

Status Recommendation:	☐ Clinical Edit ☐ Open Access	☐ PA Required ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☐ No PA Required	☒ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Atopic dermatitis (AD), the most common form of eczema, affects about 35 million people in the United States. This disease can occur at any age, but appears most often in infants and young children. According to the National Eczema Association, the prevalence of childhood AD has steadily increased from 8% to ~12% since 1997; about one-third of children with AD have moderate to severe disease. In atopic dermatitis, the skin becomes extremely itchy. Scratching leads to redness, swelling, cracking, “weeping” clear fluid, and finally, crusting and scaling. Although the cause of atopic dermatitis is unknown, certain environmental or emotional triggers, such as changes in temperature or humidity, chemical irritants, physical irritants, allergies, intense emotion/stress or infections, may cause the immune system in the skin to overreact, resulting in a “flare-up”. In the past, topical corticosteroids were the mainstay for treating eczema. However, a number of side effects including thinning of the skin, formation of dilated blood vessels and infection have been reported. The most recent guideline from the American Academy of Dermatology, published in 2014, recommends using topical tacrolimus or pimecrolimus in adults and children with atopic dermatitis in sensitive areas such as face, anogenital area or skin folds. Pimecrolimus is used for mild to moderate atopic dermatitis, while tacrolimus is used for moderate to severe atopic dermatitis.

Dosage Form [3]

Opzelura is available in a 60 g tube containing 1.5% ruxolitinib cream.

Manufacturer [3]

Distributed by: Incyte Corporation, Wilmington, DE 19803.

Indication(s) [3]

Opzelura is indicated for topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis (AD) in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Clinical Efficacy [3,4] (mechanism of action/pharmacology, comparative efficacy)

Ruxolitinib, a Janus kinase (JAK) inhibitor, inhibits JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Activation of JAK results in recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation of STATs and subsequent localization of STATs to

the nucleus leading to modulation of gene expression. Ruxolitinib selectively blocks the JAK-STAT pathway that drives itch, inflammation and skin barrier dysfunction in atopic dermatitis.

Pharmacokinetics:

Distribution	97% protein bound
Metabolism	Hepatic (CYP3A4 and to a lesser extent CYP2C9)
Excretion	Renal (74%); Fecal (22%)
Half-life	116 hours

Clinical Trials Experience

STUDY DESIGN (TRuE-AD1 and TRuE-AD2)	Two Phase 3 randomized, double-blind, vehicle-controlled studies of identical design (N=1,249; 631 in TRuE-AD1 and 618 in TRuE-AD2)

INCLUSION CRITERIA	• Patients ≥12 years
	• Diagnosis of mild or moderate AD for ≥2 years
	  ○ Affected body surface area (BSA) 3 to 20% (excluding scalp) with a mean affected BSA of 9.8%; 39% had affected areas on the face
	  ○ IGA score of 2 (mild-25%) to 3 (moderate-75%) on a severity scale of 0 to 4
	  ○ Itch Numerical Rating Scale (Itch NRS), defined as the 7-day average of the worst level of itch intensity in the last 24 hours, was 5 on a scale of 0 to 10

EXCLUSION CRITERIA	• Unstable course of AD in the 4 weeks prior to baseline • Concurrent conditions and history of other diseases: • Immunocompromised • Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline • Active acute bacterial, fungal, or viral skin infection within 1 week before baseline • Any other concomitant skin disorder, pigmentation, or extensive scarring that may interfere with the evaluation of AD lesions or compromise participant safety • Presence of AD lesions only on the hands or feet without prior history of involvement of other classical areas of involvement such as the face or folds
TREATMENT REGIMEN	Patients were randomized 2:2:1 to twice-daily, continuous treatment of the initially affected areas with 0.75% ruxolitinib cream, 1.5% ruxolitinib cream or vehicle cream in the initial 8-week portion of the study stratified by baseline Investigator's Global Assessment (IGA) score (2 or 3) and region (North America or Europe). Rescue treatment was not permitted.
RESULTS	The primary endpoint of the studies was the proportion of patients achieving IGA treatment success (IGA-TS), defined as a score of 0 [clear (minor residual discoloration)] or 1 [almost clear (faint pink erythema with almost no induration/papulation and no oozing/crusting)] with ≥2-grade improvement from baseline at week 8. The key secondary endpoints were: • Proportion of patients achieving ≥75% improvement in Eczema Area and Severity Index (EASI-75) score at week 8 • Clinically relevant reduction in itch defined as the proportion of patients with a ≥4-point reduction in itch numerical rating scale score (NRS4; measured

with worst itch level) from baseline to week 8

- Proportion of patients with a clinically meaningful improvement from baseline) in the Patient Reported Outcomes Measurement Information System short form-sleep disturbance 8(b) (PROMIS 8b) score at week 8

Patients with missing post-baseline values were considered non-responders.

Proportion of Patients Achieving Key Outcomes Measures

	Study 1			Study 2		
Endpoint	**Vehicle**	**0.75% RUX**	**1.5% RUX**	**Vehicle**	**0.75% RUX**	**1.5% RUX**
IGA-TS week 8 % (SE)	15.1 (3.2)	50.0 (3.2)‡	53.8 (3.1)‡	7.6 (2.4)	39.0 (3.2)‡	51.3 (3.3)‡
OR (95% CI)	N/A	6.4 (3.6, 11.9)	7.5 (4.2, 14.0)	N/A	8.8 (4.1, 21.2)	15.8 (7.4, 38.1)
vs Vehicle (95% CI)	N/A	34.9 (26.1, 43.7)	38.7 (29.9, 47.4)	N/A	31.3 (23.4, 39.2)	43.7 (35.6, 51.8)
EASI-75 week 8 % (SE)	24.6 (3.8)	56.0 (3.1)‡	62.1 (3.1)‡	14.4 (3.2)	51.5 (3.3)‡	61.8 (3.2)‡
OR (95% CI)	N/A	4.0 (2.4, 6.8)	5.2 (3.1, 8.8)	N/A	6.8 (3.7, 13.2)	10.7 (5.8, 20.7)
vs Vehicle (95% CI)	N/A	31.4 (21.7, 41.1)	37.5 (27.8, 47.1)	N/A	37.1 (28.1, 46.2)	47.4 (38.5, 56.4)
NRS4, % (SE)	15.4 (4.1)	40.4 (3.9)†	52.2 (3.9)‡	16.3 (4.1)	42.7 (4.0)‡	50.7 (4.1)‡
OR (95% CI)	N/A	3.7 (1.8, 8.1)	6.0 (2.9, 13.2)	N/A	4.2 (2.0, 9.0)	5.8 (2.8, 12.7)
vs Vehicle (95% CI)	N/A	25.0 (13.9, 36.1)	36.8 (25.7, 47.9)	N/A	26.4 (15.2, 37.6)	34.4 (23.0, 45.9)

‡ p <0.0001; † p<0.001

Significantly more patients reported clinically meaningful improvement in the PROMIS 8b score at week 8 with RUX cream versus vehicle (p< 0.01) in TRuE-AD1. In TRuE-AD2, the response rates were numerically higher with RUX cream versus vehicle, but the differences were not statistically significant.

SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

- **Black Box Warning-Serious Infections, Mortality, Malignancy, Major Adverse Cardiovascular Events (MACE), and Thrombosis:**
  - **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Janus Kinase inhibitors for inflammatory conditions.**
  - **Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with Janus Kinase inhibitors for inflammatory conditions.**
  - **Lymphoma and other malignancies have been observed in patients treated with Janus Kinase inhibitors for inflammatory conditions.**
  - **Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus Kinase inhibitors for inflammatory conditions.**
  - **Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with Janus Kinase inhibitors for inflammatory conditions.**
- Non-melanoma Skin Cancers: Basal cell and squamous cell carcinoma have occurred. Perform periodic examinations during treatment and following treatment as appropriate.
- Thrombocytopenia, Anemia, and Neutropenia: Thrombocytopenia, anemia, and neutropenia have occurred. Perform CBC monitoring as clinically indicated.

Adverse Effects [3,4]

Most common, ≥1%	Opzelura (N=499) n (%)	Vehicle (N=250) n (%)
Subjects with any TEAE*	132 (27)	83 (33)
Nasopharyngitis	13 (3)	2 (1)
Bronchitis	4 (1)	0 (0)
Ear infection	4 (1)	0 (0)
Eosinophil count increased	4 (1)	0 (0)
Urticaria	4 (1)	0 (0)
Diarrhea	3 (1)	1 (<1)
Folliculitis	3 (1)	0 (0)
Tonsilitis	3 (1)	0 (0)
Rhinorrhea	3 (1)	1 (<1)

* Treatment emergent adverse events

Drug Interactions [3,4]

- Drug interaction studies with Opzelura have not been conducted.

Dosage and Administration [3,4]

Apply a thin layer twice daily to affected areas of up to 20% body surface area. Do not use more than 60 g per week. For topical use only. Not for ophthalmic, oral, or intravaginal use.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Therapy
Ruxolitinib	Opzelura™	Incyte Corp.	Apply twice daily	$1,950/60 g
Crisaborole	Eucrisa®	Anacor Pharma.	Apply twice daily	$672/60 g
Pimecrolimus	Elidel®	Bausch Health	Apply twice daily	$598/60 g Brand; $322/60 g Generic
Tacrolimus	Protopic® 0.1%	LEO Pharma	Apply twice daily	$580/60 g Brand; $146/60 g Generic
Tacrolimus	Protopic® 0.3%	LEO Pharma	Apply twice daily	$580/60 g Brand; $209/60 g Generic
Doxepin	Zonalon®	Mylan Pharma.	Apply 4 times daily	$669/45 g Brand; $477/45 g Generic

** Wholesale Acquisition Cost

Conclusion

Atopic dermatitis (AD), the most common form of eczema, affects about 35 million people in the United States. This disease can occur at any age, but appears most often in infants and young children. In atopic dermatitis, the skin becomes extremely itchy. Scratching leads to redness, swelling, cracking, "weeping" clear fluid, and finally, crusting and scaling. The efficacy of Opzelura was demonstrated by two randomized, double-blind, vehicle-controlled, Phase 3 studies (TRuE AD1 and TRuE AD2). Study participants were adolescents and adults ≥12 years with mild to moderate atopic dermatitis. Data from the studies show that 53.8% and 51.3% of Opzelura-treated patients in the TRuE AD1 and TRuE AD2, respectively, met the primary endpoint at Week 8 versus 15.1% and 7.6% of vehicle-treated patients ($p<0.0001$). Opzelura carries a black box warning for serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) IPD Analytics. Available at https://secure.ipdanalytics.com
2) Formulary Decisions. Available at https://www.formularydecisions.com/Home/default.aspx?Source=HomeURL
3) Opzelura (ruxolitinib cream [prescribing information]. Wilmington, DE: Incyte Corporation; 2021.
4) Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol 2021 Oct;85(4):863-872. Available at https://www.jaad.org/article/S0190-9622(21)00931-2/fulltext

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