ruxolitinib (Jakafi®, Opzelura™)

EOCCO POLICY

Policy Type: PA /(Jakafi SP) Pharmacy Coverage Policy: EOCCO057

Description

Ruxolitinib is a Janus Associated Kinase (JAK) inhibitor of JAK1 and JAK2. Ruxolitinib (Jakafi) is orally administered, and ruxolitinib (Opzelura) is a topical cream.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indications	Quantity Limit
ruxolitinib (Jakafi)	5 mg tablets	Intermediate or high-risk myelofibrosis Polycythemia vera	60 tablets/30 days *Quantity exceptions are not allowed. *The maximum number of ruxolitinib (Jakafi) tablets allowed is 60 tablets/30 days total if a combination of strengths is used
	10 mg tablets		
	15 mg tablets		
	20 mg tablets		
	25 mg tablets		
	5 mg tablets	Acute Graft-Versus-Host Disease Chronic Graft-Versus-Host disease	
	10 mg tablets		
ruxolitinib (Opzelura)	1.5 % cream	Atopic dermatitis	2 tubes/28 days (120 grams)
		Nonsegmental Vitiligo	

**Dose optimization will be required if the prescribed dose is unable to be reached at a quantity of 60/30. Use of two strengths may be necessary to reach target dose. Quantity is subject to 30/30 if multiple tablet strengths are utilized, for a maximum total allowed quantity of 60 ruxolitinib (Jakafi) tablets per 30-day supply.*

Initial Evaluation

I. **Ruxolitinib (Jakafi)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, dermatologist, or immunologist; **AND**
   B. A diagnosis of one of the following:
      1. **Intermediate-to-high-risk myelofibrosis** which includes primary myelofibrosis, post-polycythemia vera myelofibrosis, or post essential thrombocythemia myelofibrosis; **OR**
      2. **Polycythemia vera**; **AND**
         i. Treatment with hydroxyurea has been ineffective, contraindicated, or not tolerated; **OR**

3. **Graft versus-host disease, acute or chronic; AND**
    i. Member is 12 years of age or older; **AND**
    ii. Documentation of moderate-to-severe graft versus-host disease (e.g., Grade 2 to 4, OR Grade B to D); **AND**
    iii. The member has had an inadequate response to steroids (e.g., prednisone, methylprednisolone, beclomethasone, budesonide).

II. **Ruxolitinib (Opzelura)** may be considered medically necessary when the following criteria are met:
    A. Member is 12 years of age or older; **AND**
    B. A diagnosis of one of the following:
        1. **Atopic Dermatitis; AND**
            i. Treatment with at least one agent in **ALL** of the following groups have been ineffective, contraindicated, or not tolerated:
                1. Group 1: topical corticosteroids (e.g., hydrocortisone, desonide, triamcinolone, betamethasone, clobetasol)
                2. Group 2: topical calcineurin inhibitors: tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel)
                3. Group 3: topical phosphodiesterase 4 inhibitor: crisaborole (Eucrisa); **AND**
            ii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib [Cibinqo]).
        2. **Nonsegmental Vitiligo; AND**
            i. Chronic disease (greater than 6 months); **AND**
                a. A total body surface area that does not exceed 10%; **OR**
                b. Involves areas of the face, ears, or genitalia; **AND**
            ii. Treatment with at least one therapy in **EACH** of the following categories has been ineffective or not tolerated, or are contraindicated:
                a. Phototherapy (UVB or PUVA); **AND**
                b. Topical calcineurin inhibitors: tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel); **AND**
                c. Topical corticosteroids of at least high potency (e.g., betamethasone, mometasone, clobetasol, fluocinonide); **AND**
            iii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with other biologics, systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib [Cibinqo]), or potent immunosuppressants (e.g., azathioprine, cyclosporine).

III. Ruxolitinib (Jakafi, Opzelura) is considered investigational when used for all other conditions, including but not limited to:
    A. Low risk myelofibrosis

B. Acute leukemia
C. COVID-19
D. Alopecia areata
E. Other vitiligo diseases outside of nonsegmental, or other depigmentation disease
F. Glioma and glioblastoma
G. Hidradenitis suppurativa
H. Malignancy or cancer outside of myelofibrosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. For **intermediate- to high-risk myelofibrosis OR polycythemia vera:**
    A. Request is for ruxolitinib (Jakafi); **AND**
        1. Documentation of reduction in spleen volume; **OR**
        2. Provider attestation of positive treatment response (e.g., improvement in symptoms, hematocrit control); **OR**
IV. For **graft versus-host disease, acute or chronic:**
    A. Request if for ruxolitinib (Jakafi); **AND**
        1. Provider attestation of positive treatment response (e.g. reduction in symptoms associated with graft versus-host disease: gastrointestinal, ophthalmic, cutaneous, pulmonary); **OR**
V. For **atopic dermatitis:**
    A. Request is for ruxolitinib (Opzelura) topical treatment:
        1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, reduction in BSA involvement, pruritis symptom reduction); **AND**
        2. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib).
VI. For **nonsegmental vitiligo:**
    A. Request is for ruxolitinib (Opzelura) topical treatment:
        1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in F-VASI and/or T-VASI score from baseline, reduction in BSA involvement, depigmentation reduction); **AND**
        2. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with other biologics, systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib [Cibinqo]), or potent immunosuppressants (e.g., azathioprine, cyclosporine).

Supporting Evidence

I. Length of authorization for initial approval is six months due to the clinical trial design; efficacy was evaluated at 24 weeks or less for all indications. Additionally, therapy beyond six months of treatment should be reserved for those where benefits outweigh the risks. For ruxolitinib (Jakafi) If no treatment response is seen at six months, therapy should be tapered into discontinuation. Therapy should not be abruptly discontinued given the potential for symptom proliferation and exacerbation.

II. The FDA-approved conditions for this therapy require specialized and individualized care and monitoring; thus, a specialist prescriber, or consultation with a specialist, is required.

III. Treatment for MF is based on risk. For intermediate-to high-risk MF, stem cell transplant is the recommended treatment option; however, for those ineligible for stem cell transplant, hydroxyurea, fedratinib (Inrebic), and ruxolitinib (Jakafi) are available treatment options. While hydroxyurea may relieve splenomegaly and some symptoms of the condition (e.g., thrombocytosis, leukocytosis), it is thought to be less efficacious than other treatment options and may not be beneficial for major symptoms of the condition.

IV. Polycythemia vera treatment selection is also based on risk. Phlebotomy and/or low-dose aspirin are used in the management of low-risk disease. For high-risk disease, hydroxyurea is the preferred therapy given the extensive history of use, well-established safety profile, efficacy, and cost-effectiveness. Although busulfan has been used historically as a second-line therapy, because it has been associated with safety concerns such as cytopenia, pulmonary fibrosis, leukemia, and others, hydroxyurea remains the mainstay therapy. Ruxolitinib (Jakafi) is reserved for those that are not candidates for, or are refractory to, hydroxyurea, given the limited long-term safety and efficacy data. Additionally, for the treatment of polycythemia vera, ruxolitinib (Jakafi) is specifically FDA-approved after inadequate response or intolerance to hydroxyurea.

V. The FDA approval of ruxolitinib (Jakafi) in the setting of intermediate-to high-risk myelofibrosis was based on the results of two randomized Phase 3 trials. In Study 1, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 24. Secondary outcomes included proportion of patients achieving a 50% or greater reduction in Total Symptom Score from baseline to week 24. This was measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF), which incorporates abdominal discomfort, pain, night sweating, itching, bone and muscle pain, and early satiety. The study met statistical significance in all outcomes. In Study 2, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 48. This outcome was statistically significant.

VI. The FDA approval of ruxolitinib (Jakafi) in the setting of polycythemia vera was based on the result of a randomized, open-label, active-controlled Phase 3 study. The primary endpoint was the proportion of participants at Week 32 achieving hematocrit control in the absence of phlebotomy and spleen volume reduction. In the ruxolitinib (Jakafi) arm, 60% of the participants

met the primary endpoint compared to 19% in the placebo arm. Participants must have had a resistance or intolerance to hydroxyurea.

VII. Graft-versus-host disease is a complication of allogenic hematopoietic cell transplant. Treatment is dependent on severity and location of disease. The GVHD Grade depends on severity and location, and ranges from I-IV. Grade I is reflective of skin involvement, Grade IV is severe disease with severe skin involvement (e.g., blistering) and internal organ involvement, and Grade II-IV correlates with moderate to severe disease. The International Bone Marrow Transplant Registry Severity Index uses Grade A-D, which aligns with grading I-IV.

VIII. For Grade I or A, or mild disease, topical therapy is indicated. For Grade II or B or greater, or moderate-to-severe disease, systemic therapy is warranted. Glucocorticoids are the mainstay therapy; however, for those with glucocorticoid resistant disease, participation in clinical trials is recommended as there is currently no consensus on standard of care. Otherwise, therapies such as ruxolitinib (Jakafi) or ibrutinib (Imbruvica) are recommended. Therapy such as mycophenolate, rituximab, etanercept (Enbrel), everolimus, and others have been used historically, but there is lack safety and efficacy data from clinical trials to support the use of these therapies.

IX. The FDA approval of ruxolitinib (Jakafi) in the setting of acute GVHD was based on the results of an open-label, single-arm, multicenter study in participants with steroid-refractory acute GVHD Grades II to IV that were 12 years of age or older. Therapy was evaluated up to 10 mg twice daily. The efficacy of ruxolitinib (Jakafi) was based on a Day-28 overall response rate (ORR) by the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria and the duration of response. The ORR was 57.1% with a median duration response of 16 days.

X. For chronic GVHD, ruxolitinib (Jakafi) was evaluated in a Phase 3, open-label, randomized trial against best available treatment (BAT). Patients were 12 years of age or older, steroid-refractory, and had moderate-to-severe disease. Outcomes were ORR, failure-free survival (FFS), and Lee Symptom Score. Ruxolitinib (Jakafi) was superior to BAT in all outcomes. Given the availability of objective and subjective positive outcomes in this condition, and lack of standard of care beyond glucocorticoids, there is moderate confidence that ruxolitinib (Jakafi) provides clinical value for this condition.

XI. To date, ruxolitinib (Jakafi) has not been shown to improve survival for any condition.

XII. The safety and efficacy of ruxolitinib (Jakafi), or any other JAK inhibitor has not been evaluated in patients under 12 years of age.

XIII. Split fill applies to ruxolitinib (Jakafi) given the high rates of treatment discontinuation due to adverse events, and the rates of dose reduction or interruption seen in clinical trials (e.g., in the pivotal trial for aGVHD the rate of treatment discontinuation due to adverse events was 31%).

XIV. Topical ruxolitinib is the first non-oral JAK inhibitor for the treatment of atopic dermatitis (AD). Emerging data are showing JAK inhibitors to be effective therapies; however, competing JAK therapies are oral systemic treatments: abrocitinib, upadacitinib (Rinvoq), and baricitinib (Olumiant).

XV. Nonpharmacologic treatment options for mild-to-moderate AD include emollients, wet wrap therapy, and phototherapy. Topical pharmacologic treatment options include corticosteroids (TCS), calcineurin inhibitors (TCI) (e.g., tacrolimus, pimecrolimus), and phosphodiesterase-4 inhibitor crisaborole (Eucrisa). Choice of therapy is dependent on severity, location, and other patient factors (e.g., allergies, age).

XVI. Ruxolitinib (Opzelura) was evaluated in two Phase 3, randomized, double-blind, vehicle-controlled studies in 872 adolescents and adults (TRuE-AD1 and TRuE-AD2) aged 12 and older. Treatment arms: vehicle, ruxolitinib 0.75% or 1.5%. Treatment was used continuously for eight weeks, then patients from the vehicle arm were re-randomized 1:1 to ruxolitinib 0.75% or ruxolitinib 1.5% for an additional 44 weeks. Trial population characteristics included: At least 12 years of age, 60% were female, 70% were white, had a mean affected BSA of 9-10%, baseline EASI of 8, 75% of patients had an IGA of 3, a mean NRS score of 5, median duration of AD of 16 years, and 40% of patients had facial involvement.

XVII. The primary outcome was proportion of patients achieving IGA treatment success (IGA-TS) (i.e., IGA score of 0 or 1 with at ≥ 2 grade improvement). Secondary outcomes were EASI75, change in EASI, and proportion of patients achieving ≥ 4-point improvement in the NRS itch score. At eight weeks, both ruxolitinib arms showed statistical and clinical superiority to vehicle in all outcomes. The 52-week assessments showed similar, or favorable outcomes.

XVIII. At eight weeks, rates of adverse events (AE) were similar among all treatment arms and were mild or moderate in severity. Common AEs were burning (≤ 6.5%) and pruritis (3.2%). Discontinuation rates due to AE were ≤ 4%. Safety data out to 52 weeks did not reveal additional safety warnings. No serious AE occurred as a result of ruxolitinib (Opzelura) treatment; however, there was a relatively small patient population evaluated, and with data only out to 52 weeks there may be unrealized safety characteristics. Although two clinical trials showed consistent improvement in the outcomes noted above, there remains uncertainty in the following: place in therapy, safety and efficacy data when used in combination with other topical therapies and/or systemic treatments for AD, long term safety, durability of efficacy, and comparative efficacy to other topical agents. The safety and efficacy profiles of other topical therapies are well established, and data are lacking to show superior safety and efficacy of ruxolitinib (Opzelura) over these agents. Furthermore, there is lack of safety and efficacy data in pediatric patients under 12 years of age. Other topical therapies have been approved in this age group, and ruxolitinib is being evaluated in this population.

XIX. The safety profile of systemic JAKs is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib (Opzelura) is unknown at this time, given the short trial duration and relatively small trial population. Utilizing systemic JAK therapy in addition to topical JAK therapy has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use will be disallowed. For those in need of systemic and topical therapy, provider and patients should consider therapies and combination with alternative mechanisms, including, but not

limited to, dupilumab, tralokinumab systemic therapies, and the aforementioned topical therapies.

XX. Ruxolitinib (Opzelura) 1.5% topical cream is FDA-approved at a maximum of 60 grams per week, and medication should not be applied to greater than 20% of the body surface area when utilizing for atopic dermatitis. Additionally, therapy should be used for short term and non-continuous treatment of mild to moderate atopic dermatitis. A quantity limit of two tubes (120 gams total) per 28-day supply should be sufficient or better for the majority of patients to utilize this therapy. Upon initial trial of medication, quantity limits will be set at two tubes per 28-day supply to ensure appropriate utilization within FDA label (e.g., non-continuous use), as well as ensure patients realize efficacy with medication and to minimize medication waste in the event therapy is not effective.

XXI. Ruxolitinib (Opzelura) was evaluated in two phase 3, randomized, double-blind, vehicle-controlled studies in 674 adolescents and adults (TRuE-V1 and TRuE-V2) aged 12 and older. Treatment arms: vehicle, ruxolitinib 1.5%. Subjects were randomized 2:1 of ruxolitinib to vehicle and used continuously twice a day for 24 weeks, then an additional 28-week extension where all subjects received ruxolitinib twice daily. Trial population characteristics included: At least 12 years of age, 53% were female, 82% were white, had mean depigmented areas of 1% F-BSA, mean affected total BSA of up to 7.4%, median duration of nonsegmental vitiligo of 14.8 years, and subjects were not permitted to use phototherapy during the trial period. Key inclusion criteria was a maximum BSA of 10%, which is addressed on the label as it should not be applied to greater than 10% of body surface area when utilizing for treatment of vitiligo.

XXII. The primary endpoint for both trials was percent of patients to achieve decrease of at least 75% from baseline in the facial vitiligo area scoring index (F-VASI: takes into account level of depigmentation and lesion integrity) at week 24. Secondary endpoints included a decrease of at least 50% in F-VASI, a decrease of at least 90% in F-VASI, decrease of 50% in total vitiligo area scoring index (T-VASI), change in VNS rating, and percentage change of total facial BSA affected.

XXIII. The adverse events (AE) at week 24 were similar across both treatment groups, with the most common AEs related to the trial drug were acne (5.4%) and pruritis (5.0%). Discontinuation rates from AE were <1%. Additional reporting of safety data after the extension period (week 52) found no additional safety concerns. AEs were similar to AEs noted in atopic dermatitis studies. There were 14 cases of serious AEs: 8 in the TRuE-V1 and 6 in the TRuE-V2. Review of supplemental data indicates most AEs resolved and no direct correlation to use of medication. 3 serious AEs that are ongoing include subacute cord degeneration, prostate cancer, and papillary thyroid cancer. Overall, the two trials indicated improvement in the endpoints, there is still uncertainty in place of therapy, safety and efficacy in combination with other topical therapies for vitiligo, long term safety and efficacy against other topical agents. The safety and efficacy profiles of other topical therapies are well established, and data are lacking to show superior safety and efficacy of ruxolitinib (Opzelura) over these agents. There is a lack of safety and efficacy data in pediatric patients under 12 years of age and other topical therapies have been

approved in this age group. There are ongoing extension studies assessing long term safety and efficacy past 52 weeks for 12 years of age and up but as of this time, it is not being evaluated for patients younger than 12 years of age with vitiligo.

Investigational or Not Medically Necessary Uses

I. Ruxolitinib (Jakafi, Opzelura) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Low risk myelofibrosis
   B. Acute leukemia
   C. COVID-19 or associated symptoms or complications
   D. Alopecia areata
   E. Other vitiligo diseases outside of nonsegmental, or other depigmentation disease
   F. Glioma and glioblastoma
   G. Hidradenitis suppurativa
   H. Cancer or malignancy outside of myelofibrosis

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added ruxolitinib cream (Opzelura) policy criteria and supportive evidence for use in nonsegmental vitiligo.	01/2025
Added new indication of nonsegmental vitiligo for Opzelura noting this is an excluded indication. Updated E/I language to reflect other vitiligo and depigmentation disease.	03/2023
Ruxolitinib cream added into the policy for the treatment of atopic dermatitis.	08/2021
Chronic graft vs. host disease indication added to policy. Update of qualifying prescribers and appropriate doses and quantities per indication. Removal of infection free requirement, check of unacceptable toxicity, and requirement for previous use of hydroxyurea in myelofibrosis.	06/2021
Addition of acute graft vs. host disease indication to renewal section.	01/2020
Criteria transitioned to policy. Added newly FDA approved indication of acute graft versus host disease. Remove diagnostic questions, interaction questions, lab value questions. Added requirement for previous use of hydroxyurea prior to coverage of Jakafi for the indication of polycythemia vera.	07/2019
Previous reviews	12/2014, 12/2012, 07/2012, 05/2012