

## PHARMACY COVERAGE GUIDELINE

### JAKAFI® (ruxolitinib phosphate) Generic Equivalent (if available)

#### **This Pharmacy Coverage Guideline (PCG):**

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively “Service”) is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider’s judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member’s benefit plan; and
- Is subject to change as new information becomes available.

#### **Scope**

- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

#### **Instructions & Guidance**

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The “Criteria” section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member’s benefit plan.
- The “Description” section describes the Service.
- The “Definition” section defines certain words, terms or items within the policy and may include tables and charts.
- The “Resources” section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy). You must fully complete the [request form](#) and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com).

#### **Criteria:**

- **Criteria for initial therapy:** Jakafi (ruxolitinib) and/or generic equivalent (if available) is considered **medically necessary** and will be approved when **ALL** the following criteria are met:
1. Prescriber is a physician specializing in the patient’s diagnosis or is in consultation with an Oncologist or Hematologist
  2. Individual has a confirmed diagnosis of **ONE** of the following:
    - a. Treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in an individual 18 years of age or older

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- b. Treatment of polycythemia vera (PV) in an individual 18 years of age or older who has failure, contraindication or intolerance to hydroxyurea
  - c. Treatment of Hematopoietic Cell Transplantation (HCT) steroid-refractory acute graft-versus-host disease (aGVHD) in an individual 12 years of age or older
  - d. Treatment of Hematopoietic Cell Transplantation (HCT) chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in an individual 12 years or older
  - e. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A
3. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
  - a. Assess past infections, including, tuberculosis, herpes simplex, herpes zoster, and hepatitis B
  - b. Complete blood count
4. There are **NO** unresolved active infections prior to initiation of Jakafi (ruxolitinib)
5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] ([see Definitions section](#))
6. Will not be used with other Tyrosine Kinase Inhibitors or other Janus Associated Kinase Inhibitors (such as Xeljanz (tofacitinib), Xeljanz (tofacitinib) XR, Olumiant (baricitinib), Rinvoq (upadacitinib), or Inrebic (fedratinib))
7. Individual does not have ESRD (CrCl less than 15 mL/min) not requiring dialysis

**Initial approval duration:** 6 months

➤ **Criteria for continuation of coverage (renewal request):** Jakafi (ruxolitinib) and/or generic equivalent (if available) is considered **medically necessary** and will be approved when **ALL** the following criteria are met (**samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Hematologist
2. Individual's condition has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity
3. Individual has been adherent with the medication
4. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
  - a. Progressive multifocal leukoencephalopathy (PML)

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- b. Thrombocytopenia
  - c. Neutropenia
  - d. Anemia
5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] ([see Definitions section](#))
6. Agent will not be used with other Tyrosine Kinase Inhibitors or other Janus Associated Kinase Inhibitors (such as Xeljanz (tofacitinib), Xeljanz (tofacitinib) XR, Olumiant (baricitinib), Rinvoq (upadactinib), or Inrebic (fedratinib))
7. Individual does not have ESRD (CrCl less than 15 mL/min) not requiring dialysis

**Renewal duration:** 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
  2. **Off-Label Use of Cancer Medications**
- 

#### **Description:**

Jakafi (ruxolitinib) is indicated for: adult patients with intermediate or high-risk myelofibrosis (MF), including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (Post-PV MF) and post-essential thrombocythemia myelofibrosis (Post ET MF); adult polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea; and it is also indicated for patients 12 years and older with steroid-refractory acute and chronic graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy.

Jakafi (Ruxolitinib) is a kinase inhibitor of the Janus-associated kinases (JAK), JAK1 and JAK2. There are 4 known JAK: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TyK2). JAK are intracellular enzymes that transmit signals coming from cytokine or growth factor receptor interactions on the cell membrane to influence hematopoiesis and immune cell function. Receptor binding of these kinases initiates intracellular signal pathways that regulate the transcription of genes for several cell products. JAK enzymes transmit signals through pairing of JAK (such as JAK1-JAK3, JAK1-JAK2, JAK1-TyK2, and JAK2-JAK2). Within the signaling pathway, JAK phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Interruption of these signaling pathways is thought to reduce the inflammatory response. MF and PV are myeloproliferative neoplasms known to be associated with uncontrolled and overactive JAK1 and JAK2 signaling. Inhibition of this overactivity results in a decrease in the inflammatory cytokine signaling and a decrease in overproduction of cells. JAK-STAT signaling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GVHD pathogenesis.

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MF, a Philadelphia chromosome-negative chronic myeloproliferative disorder, is characterized by progressive anemia, bone marrow fibrosis, splenomegaly and constitutional symptoms. Up to 30% of patients are initially asymptomatic. Many patients present with symptoms from anemia, splenomegaly or constitutional symptoms (severe fatigue, low grade fever, pruritus, night sweats and weight loss). As the disease evolves, all patients become symptomatic due to marrow failure and increasing splenomegaly resulting in abdominal symptoms and early satiety.

Current drug therapy is palliative and efficacy is variable. Allogeneic stem cell transplantation is potentially curative but is not appropriate for all patients. Treatment for MF may include androgens, corticosteroids, erythropoiesis-stimulating agents, thalidomide, lenalidomide, and hydroxyurea. Splenectomy can be considered in transfusion dependent anemia that is refractory to drug therapy.

The International Working Group (IWG) consensus for Myelofibrosis Research and Treatment has devised an international prognostic scoring system (IPSS) that uses presenting signs and symptoms to assign risk categories. Individuals with zero (low risk), one (intermediate risk-1), two (intermediate risk-2), or  $\geq 3$  (high risk) at presentation had non-overlapping median survivals of 135, 95, 48, and 27 months, respectively. The following five adverse prognostic features were noted by the IWP IPSS: age > 65 years; presence of constitutional symptoms (weight loss >10 % from baseline, night sweats, or unexplained fever); hemoglobin <10 g/dL; leukocyte count >  $25 \times 10^9/L$ ; and circulating blast cells  $\geq 1\%$ .

PV is a chronic myeloproliferative disorder that causes the bone marrow to produce too many red blood cells. The median age at presentation is 60 years. Patients often present with either arterial or venous vascular occlusive events. The events are predominantly coronary and cerebral but can involve the skin and gastrointestinal tract. Over time PV may evolve to MF, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS). The mainstay of therapy for PV is phlebotomy which removes excess red blood cells and lowers blood viscosity. In general, the goal of phlebotomy is to keep the hematocrit below 45% in men and 42% in women. When patients remain symptomatic despite phlebotomy, other options include hydroxyurea (with or without phlebotomy), interferon alfa, thalidomide, lenalidomide, anagrelide (in certain circumstances) and rarely, chlorambucil, melphalan, or busulfan. It is estimated that 25% of PV patients remain uncontrolled despite the use of existing standard therapies.

Graft-versus host disease (GVHD) is a multisystem disorder and is a major complication of allogeneic hematopoietic cell transplant (HCT). GVHD occurs when immune cells transplanted from a non-identical donor (the graft) recognizes the transplant recipient (the host) as foreign, and as a result an immune reaction is initiated in the transplant recipient. GVHD is a syndrome of tissue inflammation and/or fibrosis affecting skin, gastrointestinal tract, liver, lungs, and mucosal surfaces.

GVHD is usually divided into acute GVHD (aGVHD) and chronic GVHD (cGVHD) based on the time of onset. Typically, aGVHD manifests as a maculopapular rash, weight loss, diarrhea, and/or hepatitis within 100 days of transplantation while cGVHD manifests as fibrosis of skin, lungs, GI tract, and soft tissues that presents at least 100 days after transplantation. However, it has been recognized that acute and chronic GVHD may occur outside of these time periods. This has led to use of clinical findings, rather than a set time, to differentiate between acute and chronic forms of GVHD. The widely accepted National Institutes of Health (NIH) consensus criteria for the diagnosis of GVHD includes an overlap syndrome in which diagnostic or distinctive features of cGVHD and aGVHD appear together.

Patients with GVHD can be classified based on the timing of presentation and the features present:

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- **Classic aGVHD** presenting within 100 days of HCT and displaying features of aGVHD. Diagnostic and distinctive features of cGVHD are not present
- **Persistent, recurrent, late onset aGVHD** presenting greater than 100 days post-HCT with features of aGVHD and diagnostic and distinctive features of cGVHD are not present
- **Classic cGVHD** presenting at any time post-HCT with diagnostic and distinctive features of cGVHD present. There are no features of aGVHD
- **Overlap syndrome** cases may present at any time post-HCT with features of both cGVHD and aGVHD. This is sometimes referred to as "acute on chronic" GVHD]

#### Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting  
[MedWatch Forms for FDA Safety Reporting | FDA](#)

#### Myelofibrosis:

These risk stratification systems have been studied and validated only in patient with PMF, but clinically have been used for stratification of patients with Post-PV MF or Post-ET MF. Novel prognostic models are being developed for risk stratification of patients with Post-PV MF or Post-ET MF

IPSS should be used at time of diagnosis, DIPSS-PLUS is preferred during the course of treatment, DIPSS can be used if karyotyping is not available

#### **International Working Group (IWG) International prognostic scoring system (IPSS):**

Risk Stratification for Myelofibrosis (IPSS)	
	Points
Age > 65 years	1
Constitutional symptoms: Weight loss > 10 % from baseline Night sweats Unexplained fever	1
Hemoglobin <10 g/dL	1
Leukocyte count > 25 X 10 <sup>9</sup> /L	1
Circulating blast cells ≥ 1%	1
Risk Group	
Low risk	0 points
Intermediate risk-1	1 point
Intermediate risk-2	2 points
High risk	3 or more points

#### **Dynamic International Prognostic System (DIPSS):**

Prognostic Variable	Points		
	0	1	2

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Age (y)	≤ 65	> 65	
Constitutional symptoms (Y/N)	N	Y	
Hemoglobin (g/dL)	≥ 10		< 10
WBC (x 10 <sup>9</sup> /L)	≤ 25	> 25	
Peripheral blood blasts (%)	< 1	≥ 1	
Risk Group	Points		
Low	0		
Intermediate-1	1 or 2		
Intermediate-2	3 or 4		
High	5 or 6		

#### Dynamic International Prognostic System Plus (DIPSS-Plus):

Prognostic Variable	Points
DIPSS low risk	0
DIPSS Intermediate-1	1
DIPSS Intermediate-2	2
DIPSS high risk	3
Platelets < 100 x 10 <sup>9</sup> /L	1
Transfusion need	1
Unfavorable karyotype*	1
Risk Group	Points
Low	0
Intermediate-1	1
Intermediate-2	2 or 3
High	4 to 6
*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement	

#### Assessment of Symptom Burden:

MPN-SAF is recommended for assessment at baseline and MPN-SAF TSS is recommended for monitoring during the course of treatment

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)		
	Circle the one number that describes, <b>during the past week</b> , how much difficulty you had with each of the following symptoms	
Early satiety	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10

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Abdominal pain	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Abdominal discomfort	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Inactivity	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Problems with headaches	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Problems with concentration compared to before Dx	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Dizziness/vertigo/lightheaded	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Numbness tingling hands/feet	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Difficulty sleeping	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Depressed or sad mood	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Problems with sexual desire or ability	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Cough	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Night sweats	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Itching	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Bone pain – not joint pain or arthritis	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Unintentional weight loss	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Fever	Absent = 0; Daily = 10	0-1-2-3-4-5-6-7-8-9-10
Overall quality of life	As good as it can be = 0; As bad as it can be = 10	0-1-2-3-4-5-6-7-8-9-10

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS; MPN 10)		
Rate fatigue (weariness, tiredness) that describes your worst level of fatigue <b>during the past 24 hours</b>	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Circle the one number that describes, <b>during the past week</b> , how much difficulty you had with each of the following symptoms		
Early satiety	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Abdominal discomfort	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Inactivity	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Problems with concentration compared to before Dx	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Numbness tingling hands/feet	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
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Itching	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Bone pain – not joint pain or arthritis	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Unintentional weight loss	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Fever	Absent = 0; Daily = 10	0-1-2-3-4-5-6-7-8-9-10

### Polycythemia vera:

Low-risk patients

Age < 60 years

No history of thrombosis

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#### High-risk patients:

- Age  $\geq$  60 years
- History of thrombosis

#### Potential indications for cytoreductive therapy:

- New thrombosis or disease related major bleeding
- Frequent and/or persistent need for phlebotomy, but with poor tolerance for phlebotomy
- Splenomegaly
- Thrombocytosis
- Leukocytosis
- Disease related symptoms (e.g., pruritus, night sweats, fatigue)

#### Mount Sinai Acute GVHD International Consortium (MAGIC):

Organ Severity Stage	MAGIC Criteria
Skin	
0	No rash
1	Maculopapular rash < 25% BSA
2	Maculopapular rash 25-50% BSA
3	Maculopapular rash > 50% BSA
4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% BSA
Liver	
0	Total serum bilirubin < 34 micromol/L (< 2 mg/dL)
1	Total serum bilirubin 34-50 micromol/L (2-3 mg/dL)
2	Total serum bilirubin 51-102 micromol/L (3.1-6 mg/dL)
3	Total serum bilirubin 103-255 micromol/L (6.1-15 mg/dL)
4	Total serum bilirubin > 255 micromol/L (> 15 mg/dL)
Upper GI	
0	No or intermittent <sup>a</sup> anorexia or nausea or vomiting
1	Persistent <sup>a</sup> anorexia or nausea or vomiting
Lower GI	
0	Diarrhea < 500 mL/day or < 3 episodes/d for adult <sup>b,c</sup>
1	Diarrhea 500-999 mL/day or 3-4 episodes/d for adult <sup>b,d</sup>
2	Diarrhea 1000-1500 mL/day or 5-7 episodes/d for adult <sup>b,e</sup>
3	Diarrhea > 1500 mL/day or > 7 episodes/d for adult <sup>b,f</sup>
4	Severe abdominal pain with or without ileus or grossly bloody stools regardless of stool volume
<sup>a</sup> To be suggestive for GVHD: anorexia should be accompanied by weight loss, nausea should be at least 3 days, or be accompanied by at least 2 vomiting episodes per day for at least 2 days <sup>b</sup> One episode of diarrhea is considered to be about 200 mL for an adult and 3 mL/kg for a child (< 50 kg)	

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<sup>c</sup>Diarrhea < 10 mL/kg/day or < 4 episodes/day for children

<sup>d</sup>Diarrhea 10-19.9 mL/kg/day or 4-6 episodes/day for children

<sup>e</sup>Diarrhea 20-30 mL/kg/day or 7-10 episodes/day for children

<sup>f</sup>Diarrhea > 30 mL/kg/day or > 10 episodes/day for children

Stage	Skin (active erythema only)	Liver (total bilirubin)	Upper GI	Lower GI (stool output)
0	No active (erythematous) GVHD rash	< 34 µmol/L (< 2 mg/dL)	No or intermittent <sup>a</sup> anorexia or nausea or vomiting	< 500 mL/day or < 3 episodes/d for adult < 10 mL/kg/day or < 4 episodes/day for children <sup>b</sup>
1	Maculopapular rash < 25% BSA	34-50 µmol/L (2-3 mg/dL)	Persistent <sup>a</sup> anorexia or nausea or vomiting	500-999 mL/day or 3-4 episodes/d for adult <sup>b</sup> 10-19.9 mL/kg/day or 4-6 episodes/day for children
2	Maculopapular rash 25-50% BSA	51-102 µmol/L (3.1-6 mg/dL)	--	1000-1500 mL/day or 5-7 episodes/d for adult <sup>b</sup> 20-30 mL/kg/day or 7-10 episodes/day for children
3	Maculopapular rash > 50% BSA	103-255 µmol/L (6.1-15 mg/dL)	--	> 1500 mL/day or > 7 episodes/d for adult <sup>b</sup> > 30 mL/kg/day or > 10 episodes/day for children
4	Generalized erythroderma (> 50% BSA) plus bullous formation & desquamation > 5% BSA	> 255 µmol/L (> 15 mg/dL)	--	Severe abdominal pain with or without ileus or grossly bloody stools regardless of stool volume
<sup>a</sup> To be suggestive for GVHD: anorexia should be accompanied by weight loss, nausea should be at least 3 days, or be accompanied by at least 2 vomiting episodes per day for at least 2 days				
<sup>b</sup> One episode of diarrhea is considered to be about 200 mL for an adult and 3 mL/kg for a child (< 50 kg)				
Overall clinical grade (based upon most severe target organ involvement):				
Grade 0: No stage 1–4 of any organ Grade I: Stage 1–2 skin without liver, upper GI or lower GI involvement Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI Grade III: Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI				

#### **NCCN recommendation definitions:**

##### Category 1:

Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

##### Category 2A:

Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

##### Category 2B:

Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

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#### Category 3:

Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

#### Resources:

Jakafi (ruxolitinib) product information, revised by Incyte Corporation. 03-2023. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed February 21, 2025.

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