BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

INREBIC® (fedratinib)
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. 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.

Criteria:

➢ **Criteria for initial therapy:** Inrebic (fedratinib) 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 is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Intermediate-2 (INT-2) or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)

b. 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

4. 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. Thiamine level if low thiamine supplementation has been started
   b. Amylase
   c. Lipase
   d. Eastern Cooperative Oncology Group (ECOG) performance score 0-2

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 in an individual with thiamine deficiency

7. Will not be used with other Janus Associated Kinase Inhibitors (such as Jakafi (ruxolitinib), Xeljanz (tofacitinib), Xeljanz (tofacitinib) XR, Olumiant (baricitinib), Rinvoq (upadacitinib), Ojjaara (momelotinib), Vonjo (pacritinib), or others)

8. Individual is not currently taking any other drugs which cause severe adverse reactions or any significant drug interactions requiring discontinuation such as strong and moderate CYP3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort, fluconazole, erythromycin, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Inrebic (fedratinib) 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 **TWO** of the following:
   a. At least a 50% reduction in symptoms using MPN-SAF TSS
   b. At least a 35% reduction in spleen volume (by MRI or CT) **OR** at least a 50% decrease in palpable spleen length below costal margin
   c. Does not require phlebotomy

3. Individual has been adherent with the medication.

4. **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)

5. Individual is using a dose of at least 200 mg daily.

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Wernicke's encephalopathy
    b. Encephalopathy
    c. Severe to life-threatening elevation of ALT/AST that has recurred after dose interruption and dose reduction

7. Will not be used in an individual with thiamine deficiency.

8. Will not be used with other Janus Associated Kinase Inhibitors (such as Jakafi (ruxolitinib), Xeljanz (tofacitinib), Xeljanz (tofacitinib) XR, Olumiant (baricitinib), Rinvoq (upadactinib), Ojjaara (momelotinib), Vonjo (pacritinib), or others)

9. Individual is not currently taking any other drugs which cause severe adverse reactions or any significant drug interactions requiring discontinuation such as strong and moderate CYP3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort, fluconazole, erythromycin, others)

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:

Inrebic (fedratinib) is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

Fedratinib is a kinase inhibitor with activity against both wild-type and mutated Janus-associated kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). Fedratinib is selective for JAK2, with higher inhibitory activity for JAK2 (versus JAK1, JAK3, and TYK2). Abnormal JAK2 activation is associated with myeloproliferative neoplasms, including myelofibrosis and polycythemia vera. Fedratinib reduces phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibits cell proliferation, and induces apoptosis in mutated JAK2 and FLT3 cell lines, improving WBC counts, hematocrit, splenomegaly, and fibrosis

Myelofibrosis (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 ≥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 X 10^9/L; and circulating blast cells ≥ 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.

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 10^9/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
Age (y)	≤ 65	> 65	
Constitutional symptoms (Y/N)	N	Y	
Hemoglobin (g/dL)	≥ 10		< 10
WBC (x 10^9/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 10^9/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

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Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)		
	Circle the one number that describes, **during the past week**, 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 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 **during the past 24 hours**	Absent = 0; Worst imaginable = 10	0-1-2-3-4-5-6-7-8-9-10
Circle the one number that describes, **during the past week**, 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
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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

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

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.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Resources:

Inrebic (fedratinib) product information, revised by Celgene Corporation 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 15, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myeloproliferative Neoplasms Version 2.2024– Updated August 08, 2024. Available at https://www.nccn.org. Accessed October 15, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 2.2024 – Updated June 19, 2024. Available at https://www.nccn.org. Accessed October 15, 2024.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.