BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/21/2019
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INREBIC® (fedratinib)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

INREBIC® (fedratinib)

Criteria:

- **Criteria for initial therapy:** Inrebic (fedratinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in patient's diagnosis or is in consultation with an Oncologist or Hematologist

  2. Individual is 18 years of age or older

  3. 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) and **ANY** of the following:

     b. Treatment for myeloid/lymphoid neoplasms with eosinophilia and JAK2 rearrangement in chronic phase

     c. Treatment in combination with ALL- or AML-type induction chemotherapy followed by allogeneic HCT (if eligible) for lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and JAK2 rearrangement in blast phase

     d. 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. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Thiamine level
     b. Complete blood count with platelets
     c. Hepatic function tests
     d. Amylase
     e. Lipase
     f. Creatinine and blood urea nitrogen (BUN)
     g. Eastern Cooperative Oncology Group (ECOG) performance score 0-1

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

  6. Individual does not have severe hepatic impairment

  7. Will not be used with Jakafi (ruxolitinib), Olumiant (baricitinib), Xeljanz (tofactinib), Xeljanz XR (tofactinib), or Rinvoq (upadactinib)

  Initial approval duration: 6 months

INREBIC® (fedratinib)

- **Criteria for continuation of coverage (renewal request):** Inrebic (fedratinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in patient's diagnosis or is in consultation with an Oncologist or Hematologist

2. Individual's condition responded or has not worsened while on therapy
    a. Response is defined as **TWO** of the following:
        i. No evidence of disease progression
        ii. At least a 50% reduction symptoms using MPN-SAF TSS
        iii. 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
        iv. Does not require phlebotomy
    b. Worsening is defined as:
        i. No evidence of reduction in spleen size **OR** no symptom improvement

3. Individual has been adherent with the medication

4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Wernicke's encephalopathy
        ii. Encephalopathy
        iii. Thrombocytopenia
        iv. Bleeding
        v. Neutropenia
        vi. Anemia
        vii. GI toxicity
        viii. Hepatotoxicity

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

6. Individual does not have severe hepatic impairment

7. Will not be used with Jakafi (ruxolitinib), Olumiant (baricitinib), Xeljanz (tofactinib), Xeljanz XR (tofactinib), or Rinvoq (upadactinib)

8. There are no significant interacting drugs

Renewal duration: 12 months

INREBIC® (fedratinib)

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.

INREBIC® (fedratinib)

Definitions:

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		

INREBIC® (fedratinib)

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

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

INREBIC® (fedratinib)

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
Numbness tingling hands/feet	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
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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

Resources:

Inrebic (fedratinib) product information, revised by manufacturer 08-2019, at DailyMed http://dailymed.nlm.nih.gov accessed 08-31-20

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myeloproliferative Neoplasms Version 1.2020 – Updated May 21, 2020 ; https://www.nccn.org. Accessed August 31, 2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 3.2021 – Updated August 21, 2020 ; https://www.nccn.org. Accessed August 31, 2020

Tefferi A. Overview of the myeloproliferative neoplasms. In: UpToDate, Larson RA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com (Accessed on August 31, 2020)

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.