09-J3000-49

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Next Review: 03/08/23

Subject: Fedratinib (Inrebic) capsules

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DESCRIPTION:

Myelofibrosis, a myeloproliferative neoplasm, can present as a primary disease or can evolve from polycythemia vera or essential thrombocytopenia. It is characterized by marrow fibrosis, progressive anemia, and extramedullary hematopoiesis and manifests primarily as splenomegaly. Myelofibrosis manifests as debilitating symptoms (e.g., fatigue, weakness, abdominal pain, cachexia, weight loss, pruritus, night sweats, and bone pain), which are thought to be the combined effects of massive splenomegaly and elevated levels of proinflammatory cytokines. Traditional therapeutic options, including splenectomy, have demonstrated only limited benefit and although allogeneic stem-cell transplant may cure myelofibrosis, few individuals are eligible for this treatment. It is hypothesized that the pathogenesis of myelofibrosis is related to direct or indirect activation of the intracellular Janus kinase (JAK) signal transducer and activator transcription (STAT) pathway. Additionally, proinflammatory cytokines that play an important role in myelofibrosis signal through JAK 1 (JAK1) AND JAK2.

Fedratinib (Inrebic®) is an oral kinase inhibitor with selective activity against JAK2 and FMS-like tyrosine kinase 3 (FLT3). It is Food and Drug Administration (FDA) approved for the treatment of adults with intermediate-2 or high-risk primary or secondary [post-polycythemia vera (post-PV) or post-essential thrombocythemia(post-ET)] myelofibrosis (MF). The safety and efficacy of fedratinib was evaluated in a double-blind, randomized, placebo-controlled trial in patients with splenomegaly and intermediate-2 or high-risk primary MF, or post-PV-MF or post-ET-MF. Eligible patients had a platelet count of greater than or equal to 50 x 10^9/L and no splenectomy. There were 289 patients randomized to receive fedratinib or placebo; fedratinib was provided at a dose of either 400 mg or 500 mg once daily for at least 24 weeks. The primary endpoint was the proportion of patients with a 35% reduction from baseline in spleen volume at the end of 24 weeks as measured by MRI or CT. The main secondary end point was the proportion of patients with a greater than or equal to 50% improvement in the 6 core MF symptoms

(i.e., night sweats, itching, abdominal discomfort, early satiety, pain under the ribs on left side, and bone or muscle pain) as assessed using the Myelofibrosis Symptom Assessment Form (MFSAF v2.0). The proportion of patients with greater than or equal to 35% reduction in spleen volume was 37% (n=35) in the fedratinib 400 mg group as compared to 1% (n=1) in the placebo group. The proportion with greater than or equal to 50% improvement in the MFSAF at the end of 6 months was 40% (n=36) in the fedratinib 400 mg group as compared to 9% (n=7) in the placebo group. Serious adverse events including Wernicke's encephalopathy occurred in 4 patients receiving fedratinib 500 mg. Common adverse reactions that occurred were gastrointestinal symptoms (diarrhea, nausea, vomiting), anemia, thrombocytopenia, and increased lab values such as liver transaminases, serum creatinine and pancreatic enzymes. Fedratinib was also assessed in a single-arm trial in patients with ruxolitinib resistant or intolerant intermediate or high-risk primary MF, post-PV-MF or post-ET-MF. Similar results in efficacy occurred with 55% (n=46) of patients experiencing a greater than or equal to 35% reduction in spleen volume as compared to baseline.

National Comprehensive Cancer Network (NCCN) Guidelines recommend fedratinib for the treatment of myelofibrosis and myeloid and/or lymphoid neoplasms with eosinophilia and JAK2 rearrangement.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of fedratinib (Inrebic®) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when **ALL** associated criteria are met:

1. Primary myelofibrosis (MF), post-polycythemia vera myelofibrosis (Post-PV-MF), or post-essential thrombocythemia myelofibrosis (Post-ET-MF) and **ALL** of the following:
    a. The member had an inadequate response, intolerance, or is not a candidate for treatment with ruxolitinib (Jakafi)
    b. Member meets **ONE** of the following:
        i. Disease is classified as intermediate-2 or high-risk and **ALL** of the following:
            1. Member is not a transplant candidate
            2. Platelets are greater than 50,000
        ii. Fedratinib is used for improvement of clinical symptoms for **ONE** of the following:
            1. MF accelerated phase
            2. MF blast phase/AML
            3. MF-associated anemia

4. Higher-risk MF when used for a transplant candidate near the start of conditioning therapy

c. Dose does not exceed 400 mg per day using the fewest number of capsules per day

2. Myeloid and/or lymphoid neoplasms with eosinophilia and JAK2 rearrangement
    a. The member had an inadequate response, intolerance , or is not a candidate for treatment with ruxolitinib (Jakafi)
    b. When used for the treatment of **ONE** of the following:
        i. Chronic phase disease
        ii. Blast phase disease when used in combination with ALL- or AML- induction chemotherapy
    c. Dose does not exceed 400 mg per day using the fewest number of capsules per day
3. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. **ONE** of the following is met:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. Dose does not exceed the maximum FDA-approved dose

Approval duration: 180 days

Continuation of fedratinib (Inrebic®) meets the definition of medical necessity for MF, Post-PV-MF, Post-ET-MF, Myeloid and/or lymphoid neoplasms with eosinophilia and JAK2 rearrangement, and other FDA-approved or NCCN supported diagnosis when **ALL** of the following criteria are met:

1. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage
2. The member has experienced a beneficial response to therapy (e.g., reduction in spleen size, improvement in clinical symptoms)
3. The dose does not exceed 400 mg per day using the fewest number of capsules per day

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF): 400 mg once daily with or without food if the platelet count is greater than or equal to 50 x 10^9/L. Prior to treatment assess thiamine, CBC with platelets, creatinine and BUN, hepatic panel, amylase and lipase.

Dose Adjustments

- Reduce dose for patients taking strong CYP3A inhibitors to 200 mg once daily. See prescribing information for dosage increase following discontinuation
- Reduce dose to 200 mg for patients with severe renal impairment (CrCl 15 mL/min to 29 mL/min)
- Modify dose for hematologic and non-hematologic adverse reactions. Discontinue for patients unable to tolerate 200 mg daily. See prescribing information.

Drug Availability

- 100 mg capsules

PRECAUTIONS:

Boxed Warning

- Serious and fatal encephalopathy, including Wernicke's, has occurred and is a neurologic emergency. Assess thiamine levels prior to initiation, during treatment and as clinically indicated. Do not initiate in the setting of thiamine deficiency; replete thiamine prior to initiation. If encephalopathy is suspected, immediately discontinue treatment and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

Contraindications

- None

Precautions/Warnings

- Anemia and Thrombocytopenia: Manage by dose reduction, interruption, or transfusion
- Gastrointestinal Toxicity: Manage by dose reduction or interruption if patient develops severe diarrhea, nausea, or vomiting. Prophylaxis with anti-emetics and treatment with anti-diarrhea medications are recommended.
- Hepatic Toxicity: Manage by dose reduction or interruption
- Amylase and Lipase Elevation: Manage by dose reduction or interruption
- Major Adverse Cardiac Events (MACE): Monitor for development of MACE
- Thrombosis: Evaluate and treat symptoms of thrombosis promptly
- Secondary Malignancies: Monitor for development of secondary malignancies, particularly in patients who are current or past smokers.
- Avoid use with strong and moderate CYP3A4 Inducers
- Avoid use with dual CYP3A4 and CYP2C19 inhibitors

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals
J8999	Prescription drug, oral, chemotherapeutic, not otherwise specified

ICD-10 Diagnoses Codes That Support Medical Necessity

C94.40 – C94.42	Acute panmyelosis with myelofibrosis
C94.6	Myelodysplastic disease, not classified
C94.8 –C94.82	Other specified leukemias
C95.1 – C95.12	Chronic leukemia of unspecified cell type
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.9	Malignant of neoplasm of lymphoid, hematopoietic and related tissue, unspecified
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D75.81	Myelofibrosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Essential thrombocythemia: an increased number of thrombocytes (platelets) in the blood, without a known cause. Also called essential thrombocytosis.

International Prognostic Scoring System for myelofibrosis: mechanism for assessing a member's prognosis at the time of diagnosis; assigns a value of 1 for each prognostic factor (Table 4). A score of 0 is indicative of low risk, 1 is indicative of intermediate-1 risk, 2 intermediate-2 risk, and 3 or more points is indicative of high risk. The risk group corresponds to a median overall survival that ranges from 2.25 years (high risk) to 11.25 years (low risk); Individuals classified as intermediate-1 or intermediate-2 have an estimated median survival of 7.92 and 4 years, respectively.

Table 1

Prognostic factors

IPSS Risk Factors
Age greater than 65
WBC greater than 25,000
Hemoglobin less than 10 g/dL
Peripheral blood blasts 1% or greater
Constitutional symptoms

Myelofibrosis: myeloproliferative disease in which the proliferation of an abnormal type of bone marrow stem cell results in fibrosis, or the replacement of the marrow with collagenous connective tissue fibers.

Polycythemia vera: A disease in which there are too many red blood cells in the bone marrow and blood, causing the blood to thicken. The number of white blood cells and platelets may also increase. The extra blood cells may collect in the spleen and cause it to become enlarged. They may also cause bleeding problems and make clots form in blood vessels.

Primary myelofibrosis: a progressive, chronic disease in which the bone marrow is replaced by fibrous tissue and blood is made in organs such as the liver and the spleen, instead of the bone marrow. This disease is marked by an enlarged spleen and progressive anemia. Also called agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis, idiopathic myelofibrosis, and myelosclerosis with myeloid metaplasia.

Splenomegaly: enlarged spleen.

RELATED GUIDELINES:

Ruxolitinib (Jakafi) Tablets, 09-J1000-63

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/09/22.

GUIDELINE UPDATE INFORMATION:

12/15/19	New Medical Coverage Guideline.
07/15/20	Review and revision to guideline; consisting of updating the position statement and references.
04/15/21	Review and revision to guideline; consisting of updating the position statement, coding, and references.
04/15/22	Review and revision to guideline; consisting of updating warnings and references.