fedratinib (Inrebic®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO083

Description

Fedratinib (Inrebic) is an orally administered kinase inhibitor with activity against both wild-type and mutated Janus-associated kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
fedratinib (Inrebic)	Intermediate- or high-risk myelofibrosis	100 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Fedratinib (Inrebic)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. A diagnosis of **intermediate- or high-risk myelofibrosis (MF)** when the following are met:
      1. Splenomegaly is present and baseline spleen volume is documented; **AND**
      2. Documentation of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain); **AND**
      3. Platelet count, measured within the past 30 days, is greater than or equal to, 50 x 10^9/L; **AND**
      4. Treatment with ruxolitinib (Jakafi) has been ineffective or not tolerated.

II. Fedratinib (Inrebic) is considered investigational when used for all other conditions, including but not limited to:
   A. Low risk myelofibrosis
   B. Polycythemia vera
   C. Graft versus host disease
   D. Lymphoproliferative neoplasms
   E. Solid tumors (e.g., prostate, colorectal, lung)
   F. Acute myeloid leukemia (AML)
   G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
   H. COVID-19

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. A diagnosis of intermediate- or high-risk myelofibrosis (has not transformed to AML); **AND**
IV. Member has exhibited improvement in or stability of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain).

Supporting Evidence

I. Myelofibrosis (MF) is a cancer of the bone marrow. Symptoms are non-specific (e.g., fatigue, shortness of breath, bleeding) and splenomegaly is common. Over time MF may progress to acute myeloid leukemia (AML). There are five risk levels of disease that correlate with prognosis, and treatment is based on risk. When patients are not eligible for allogeneic stem cell transplant, symptom targeted therapy may be used in those with intermediate or higher risk MF. Symptomatic therapies include hydroxyurea and JAK inhibitors: ruxolitinib (Jakafi), fedratinib (Inrebic), and pacritinib (Vonjo). JAK inhibitors have only been sufficiently evaluated in patients with at least intermediate-risk MF and have unknown clinical value for lower risk disease. JAK inhibitors do not reverse fibrosis or prolong survival but may reduce spleen size and improve disease-related symptoms. In absence of splenomegaly and symptoms, these medications have unknown application. Given the specialized diagnosis, treatment, and monitoring, prescribing by, or in consultation with, a specialist is required.
II. Fedratinib (Inrebic) and ruxolitinib (Jakafi) are approved for MF when platelet count is ≥ 50 x 10^9/L. These medications cause thrombocytopenia and are recommended to be discontinued if the platelet count drops below 50 x 10^9/L. Pacritinib (Vonjo), has a unique approval, and was approved under the accelerated approval pathway based on spleen volume reduction (SVR) when platelet count is under 50 x 10^9/L (severe thrombocytopenia). These therapies have only been evaluated in adults; use in pediatrics or adolescents has unknown value or consequences. Outside of a clinical trial setting, therapy should only be utilized in adults.
III. Fedratinib (Inrebic) was evaluated as an initial treatment in patients with intermediate-2 or high-risk MF (JAKARTA) and as a second-line treatment in patients who are ruxolitinib (Jakafi) resistant or intolerant (JAKARTA-2).
    - JAKARTA: Phase 3, double-blind, randomized, placebo-controlled trial with 289 total patients. The primary and secondary endpoints were superior to placebo: spleen volume reduction of 35% and at least a 50% reduction in total symptom score.

- JAKARTA-2: Single-arm, open-label, non-randomized, Phase 2 trial in ruxolitinib (Jakafi) resistant or intolerant patients, which showed patients were able to achieve spleen volume reduction of 35% as well as a 50% or greater reduction in TSS.
- Dose interruptions due to adverse events occurred in 21% of patients, dose reductions in 19%, and permanent discontinuation in 14%. Split-fill is applied.

IV. As of February 2022, NCCN guidelines recommend treatment with fedratinib (Inrebic) or ruxolitinib (Jakafi) in higher risk MF when platelet count is greater than 50 x 10^9/L (Category 1).

V. Fedratinib (Inrebic) has shown to reduce spleen size and improve disease-related symptoms; however, reduction of spleen volume alone without associated improvement in symptoms has unknown clinical value. Therapy should be initiated in presence of disease-related symptoms in those that are not candidates for transplant, and it is appropriate to continue treatment when therapy has stabilized or improved symptoms.

VI. Fedratinib (Inrebic) uniquely carries a black box warning for encephalopathy including Wernicke's, due to seven cases of Wernicke's encephalopathy during clinical trials. Providers should monitor patients for risk prior to starting fedratinib (Inrebic) and during therapy. In patients that have elevated risk or develop encephalopathy on treatment, alternative JAK inhibitors may be considered for use.

VII. There is no evidence of superiority for any of the three JAK inhibitors for MF; however, when balancing safety and cost effectiveness, use of ruxolitinib (Jakafi) prior to coverage consideration of fedratinib (Inrebic) is required.

Investigational or Not Medically Necessary Uses

I. Fedratinib (Inrebic) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Low risk myelofibrosis
   B. Polycythemia vera
   C. Graft versus host disease
   D. Lymphoproliferative neoplasms
   E. Solid tumors (e.g., prostate, colorectal, lung)
   F. Acute myeloid leukemia (AML)
   G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
   H. COVID-19

References

1. Inrebic [Prescribing Information]. Celgene Corporation: Summit, NJ. August 2019. Revised 12/2021

2. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf Updated February 28, 2022
3. UpToDate, Inc Management of primary myelofibrosis. UpToDate [database online]. Waltham, MA. Last updated Dec 06, 2021.Available at: http://www.uptodate.com/home/index.html.
4. Celgene Corporation [online press release]. U.S. FDA Approves INREBIC® (Fedratinib) as First New Treatment in Nearly a Decade for Patients with Myelofibrosis. Available at: https://ir.celgene.com/press-releases/press-release-details/2019/US-FDA-Approves-INREBIC-Fedratinib-as-First-New-Treatment-in-Nearly-a-Decade-for-Patients-With-Myelofibrosis/default.aspx. Updated August 16, 2019.
5. Jakafi [Prescribing Information]. Incyte Corporation: Wilmington, DE. May 2019, Revised 9/2021.
6. Pardanani A, Harrison C, Cortes JE, et al. Safety and Efficacy of Fedratinib in Patients with Primary or Secondary Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2015;1(5):643-51.
7. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. Lancet Haematol. 2017;4(7):e317-e324.
8. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.
9. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: An updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. Am J Hematol. 2020 Jun;95(6):594-603. doi: 10.1002/ajh.25777. Epub 2020 Apr 17. PMID: 32129512; PMCID: PMC7317815.
10. Vonjo [Prescribing Information]. CTI Biopharma Corp. Seattle, WA. February 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
ruxolitinib (Jakafi)	Intermediate- or high-risk myelofibrosis
	Polycythemia vera
	Graft versus-host disease (acute or chronic)
pacritinib (Vonjo)	Intermediate- or high-risk myelofibrosis

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to new formatting changes including addition of related policy. Reviewed for new indications and appropriateness of policy criteria. Updated supporting evidence. Simplified required diagnosis, to "Int. or high risk MF". Added an age edit to align with the labeled indication/age and known safety profile (i.e., adults). Added requirement of both: splenomegaly AND disease related symptoms. Added requirement of prior ruxolitinib (Jakafi) treatment. Updated renewal criteria to remove requirement of SVR reduction.	5/2022
Criteria created	9/2019