fedratinib (Inrebic®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO083

Description

Fedratinib (Inrebic) is an orally administered kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
fedratinib (Inrebic)	100 mg tablets	Myelofibrosis	120 tablets/30 days	207644

Initial Evaluation

I. Fedratinib (Inrebic) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by or in consultation with a hematologist or oncologist; **AND**
   B. A diagnosis of **intermediate- to high-risk myelofibrosis (MF)** when the following are met:
      1. The member's myelofibrosis is characterized by one of the following: primary MF, post-polycythemia vera MF, or post essential thrombocytopenia MF; **AND**
      2. Treatment with ruxolitinib (Jakafi) has been ineffective, contraindicated, or not tolerated; **AND**
      3. Starting platelet count, measured within the past 30 days, is greater than or equal to 50,000/microL (50 X 10^9/L); **AND**
      4. Baseline spleen volume has been measured and documentation has been submitted with medication request

II. Fedratinib (Inrebic) is considered investigational when used for all other conditions, including but not limited to:
   A. Symptomatic low-risk myelofibrosis (MF)
   B. Acute myeloid leukemia
   C. Polycythemia vera

Renewal Evaluation

I. Documentation of reduction in spleen volume or palpable spleen length; **AND**
II. Documentation of improvement in symptoms

Supporting Evidence

I. 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).
II. JAKARTA was a Phase 3, double-blind, randomized, placebo-controlled trial that met its primary endpoint of spleen response (defined as a >35% reduction in spleen volume from baseline as determined by magnetic resonance imaging or computed tomography) at week 24 and confirmed 4 weeks later; achieved by 36 % and 40% of patients in the fedratinib (Inrebic) 400 mg and 500 mg groups, vs 1% in the placebo group (P < .001).
    - The secondary endpoint of reduction of at least 50% in the total symptom score (TSS) from baseline to week 24 was 36%, 34%, and 7% in the 400 mg, 500 mg, and placebo groups, respectively.
III. JAKARTA-2 was a single-arm, open-label, non-randomized, Phase 2 trial in ruxolitinib (Jakafi) resistant or intolerant patients which reported a spleen response (≥35% reduction in spleen volume from baseline) in 46 (55%, 95% CI 44–66) of 83 patients at week 24.
    - The secondary endpoint of reduction of at least 50% in the total symptom score from baseline to week 24 was achieved in 26% of patients (23 of 90 evaluable for symptom response).
IV. Though patients in the clinical trials were previously on hydroxyurea, hydroxyurea does not play a role in the treatment of an intermediate-2 or high-risk myelofibrosis patient as its benefits are minimal. It is typically used in patients who have thrombocytosis/and are ineligible for ruxolitinib (Jakafi). However, anemia is worsened by this agent and will prevent most patients from being able to utilize it. Additionally, NCCN states that hydroxyurea has only a limited role in a patient who may benefit from cytoreduction in the low-risk category. Therefore previous treatment with hydroxyurea is not required in the intermediate-2 or high-risk myelofibrosis setting.
V. As of September 2019, NCCN guidelines recommend treatment with fedratinib (Inrebic) in patients with intermediate-2 or high-risk MF and a platelet count greater than 50,000 microL (category 2B recommendation) or in those with no response or loss of response to ruxolitinib (Jakafi) (category 2A recommendation).
VI. Unlike ruxolitinib (Jakafi), fedratinib (Inrebic) carries a black box warning for encephalopathy including Wernicke's, due to seven cases of Wernicke's encephalopathy during fedratinib (Inrebic) trials. As a result the fedratinib (Inrebic) program was previously placed on clinical hold.

VII. There is currently no evidence that fedratinib (Inrebic) is superior to ruxolitinib (Jakafi) as initial therapy for the treatment of myelofibrosis. As noted above NCCN guidelines provide ruxolitinib (Jakafi) a 2A recommendation in the first line setting and fedratinib (Inrebic) a 2B. Ruxolitinib (Jakafi) has a longer time on the market providing a more clear safety picture and through additional studies has been shown to improve survival in this disease state. Additionally, the treatment paradigm of using ruxolitinib (Jakafi) in the first line setting allows members to have a second-line option with fedratinib (Inrebic). As JAKARTA-2 indicates fedratinib (Inrebic) has activity in ruxolitinib (Jakafi) resistant patients, but there is no evidence to say the reverse is true. Lastly, the cost of one year of treatment with ruxolitinib (Jakafi) is approximately $159,517, while the cost of fedratinib (Inrebic) is $255,500.

VIII. During the JAKARTA trial, fedratinib (Inrebic) showed dose interruptions due to adverse events in 21% of patients, dose reductions in 19%, and permanent discontinuation in 14% of patients.

IX. NCCN guidelines recommend consideration of clinical trial participation in patients with platelet counts less than 50, 000/microL. Guidelines state that patients with a platelet count less than 50, 000/microL experience a greater symptom burden and might benefit from symptomatically guided treatment options. However, at present time there are no effective treatment options for this group of patients since the majority of clinical trials evaluating treatment options for MF have excluded this group of patients, which is the case of fedratinib (Inrebic) trials.

Investigational or Not Medically Necessary Uses

I. Currently, there is no high-quality published clinical trial evidence supporting the safety or efficacy of fedratinib (Inrebic) in the following settings:
   A. Symptomatic low-risk myelofibrosis (MF)
   B. Acute myeloid leukemia
   C. Polycythemia vera

References

1. Inrebic [Prescribing Information]. Celgene Corporation: Summit, NJ. August 2019.
2. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Updated September 4, 2019
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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.

Policy Implementation/Update:

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Last Updated	
Last Reviewed	

Action and Summary of Changes	Date