Original Effective Date: 09/01/2019
Current Effective Date: 06/23/2023
Last P&T Approval/Version: 04/26/2023
Next Review Due By: 04/2024
Policy Number: C17941-A

Inrebic (fedratinib)

PRODUCTS AFFECTED

Inrebic (fedratinib)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This 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 Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Myelofibrosis (MF)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. MYELOFIBROSIS:
1. Documented diagnosis of myelofibrosis (MF)
   AND
2. Documented GIPSS (genetically inspired prognostic scoring system) of 2 points or greater (int-2 or high risk) OR MIPSS70+ v2.0 (mutation- enhanced international prognostic scoring system

plus karyotype, version 2.0) score of 3 points or greater (intermediate, high, or very high risk) [DOCUMENTATION REQUIRED] See Appendix for scoring information
AND

3. Prescriber attests that member is ineligible for allogeneic hematopoietic cell transplantation (HCT)
AND
4. Prescriber attests that thiamine (vitamin B1) levels and nutritional status will be assessed and repleted if needed prior to initiating therapy and periodically during treatment
AND
5. Documentation of baseline assessment of disease (e.g., spleen size, symptoms, Total Symptom Score as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF))
AND
6. Documentation that baseline platelet count is ≥ 50,000/mm^3 (labs dated within the last 4 weeks)
AND
7. Prescriber attests that CBC with platelets, creatinine and BUN, hepatic panel, and amylase and lipase will be assessed at baseline and periodically during treatment
AND
8. Prescriber attests that member has tried and failed or has a labeled contraindication to Jakafi (ruxolitinib)
AND
9. Documentation member is not currently using Jakafi (ruxolitinib) or will discontinue prior to initiation of Inrebic
AND
10. Prescriber attests that member is not concurrently taking a Strong and Moderate CYP3A4 Inducers OR Dual CYP3A4 and CYP2C19 Inhibitor

CONTINUATION OF THERAPY:

A. MYELOFIBROSIS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member's medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
3. Documentation of a positive response to treatment with a decrease in spleen size or improvements in other myelofibrosis symptoms (such as fatigue, bone pain, frequent infections, fever, night sweats, easy bruising/bleeding, etc.) or reduction in the Total Symptom Score from baseline as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF)

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a hematologist or oncologist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:

400 mg orally once daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Janus Associated Kinase (JAK) Inhibitors

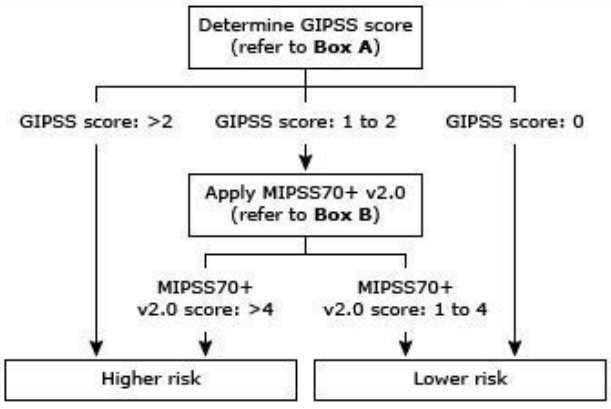
FDA-APPROVED USES:
Treatment of adult patients with intermediate-2 or high-risk primary or secondary (post- polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Risk stratification in primary myelofibrosis



Box A

GIPSS score (sum of points below):
- Karyotype:*
  - Very high risk (2 points)
  - Unfavorable (1 point)
- Driver mutations:
  - Absence of type 1-like *CALR* (1 point)
- HMR mutations:
  - *ASXL* mutation (1 point)
  - *SRSF2* mutation (1 point)
  - *U2AF1* Q157 mutation (1 point)

Box B

MIPSS70+ v2.0 score (sum of points below):
- Clinical:
  - Severe anemia: Men Hgb <9 g/dL, women Hgb <8 g/dL (2 points)
  - Moderate anemia: Men Hgb 9 to 10.9 g/dL, women Hgb 8 to 9.9 g/dL (1 point)
- Karyotype:
  - Very high risk (4 points)
  - Unfavorable (3 points)
- Mutations:
  - >1 HMR mutations (3 points)
  - 1 HMR mutation (2 point)
  - Absence of type 1-like *CALR* mutation (2 points)

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Myelofibrosis (MF) is a serious and rare bone marrow disorder that disrupts the body's normal production of blood cells. It is classified as a myeloproliferative neoplasm, a group of rare blood cancers that are derived from blood forming stem cells. Myelofibrosis occurs when bone marrow is gradually replaced with fibrous scar tissue, which limits the ability of the bone marrow to make blood cells. The disorder can lead to anemia, weakness, fatigue, and enlargement of the spleen and liver, among other symptoms. In the U.S., between 16,000 and 18,500 are living with myelofibrosis, and
1.5 of every 100,000 people will be diagnosed with myelofibrosis each year. Both men and women are affected, and while the disease can affect people of all ages, the median age at diagnosis ranges from 60 to67 years. Myelofibrosis can cause extreme fatigue, shortness of breath, pain under the ribs, fever, night sweats, itching, and bone pain. The most common presenting complaint in MF is that of severe fatigue, occurring in 50–70% of patients. Symptoms due to an enlarged spleen have been described in 25–50% of patients, while a smaller number note weight loss, and 5– 20% experience low grade fever, bone pain, and night sweats. Approximately 15–30% of patients are asymptomatic, with the diagnosis being made during investigation of splenomegaly (occurring in at least 90% of patients), hepatomegaly (40–70%), or abnormal blood findings. Other findings include but are not limited to pulmonary hypertension, pruritus, thrombotic events, portal vein thrombosis, extramedullary hematopoiesis, bone and joint involvement, and secondary gout. Relief of symptoms and improved quality of life are important goals for all patients with MF. Allogenic hematopoietic cell transplantation can prolong survival with the potential for cure. Up until the approval of Inrebic, therapy consisted of Jakafi or hydroxyurea for patients with symptomatic MF. Selection of therapy is informed by the nature and severity of symptoms, blood counts, kidney and liver function, clinician experience, and member preference. Jakafi and hydroxyurea can provide symptomatic relief, but neither agent has been proven to prolong survival or reduce the risk of leukemic transformation. Jakafi is generally considered to be more effective for relieving MF-related symptoms, but it cannot be used in patients with active infections, and it should be used with care in patients with thrombocytopenia, impaired liver or kidney function, or concurrent use of medications that are strongCYP3A4 inhibitors. In addition, it cannot be abruptly discontinued due to risk of full relapse of disease symptoms. Hydroxyurea is thought to be less effective than Jakafi, but it can relieve moderate splenomegaly and other proliferative manifestations.

Inrebic (fedratinib)/Celgene is indicated for the treatment of adult patients with intermediate-2 or high- risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) MF. Approval of Inrebic is based on findings from the double-blind, placebo-controlled Phase 3 JAKARTA trial, which included 289 patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera (PV) myelofibrosis, or post-essential thrombocytopenia (ET) myelofibrosis randomized to receive Inrebic orally at 400 (n = 96) or 500 mg daily (n = 97), or placebo (n = 96), for at least 6 consecutive 4-week cycles. The primary endpoint was spleen response, specifically a ≥35% reduction in spleen volume from baseline; a key secondary endpoint was symptom response, determined as ≥50% reduction in total symptom score assessed via the modified Myelofibrosis Symptom Assessment Form. The results demonstrated a reduction in splenomegaly and symptom burden in patients with MF. The study found that 35 of 96 patients (36%) treated with the Inrebic 400-mg daily dose experienced a 50% or greater reduction in MF related symptoms compared to 1% of patients on placebo. Additionally, Inrebic improved the Total Symptom Score by ≥50% when assessed from baseline to the end of cycle 6 in 40% of patients treated with the 400-mg dose of Inrebic versus 9% of those on the placebo arm.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Inrebic (fedratinib) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Inrebic (fedratinib) include: Use with strong and moderate CYP3A4 inducers, use with dual CYP3A4 and CYP2C19 inhibitors, patients with severe hepatic impairment (total bilirubin >3 time ULN and any AST).

OTHER SPECIAL CONSIDERATIONS:
Inrebic (fedratinib) has a Black Box Warning for ENCEPHALOPATHY INCLUDING WERNICKE'S Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with INREBIC. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency, replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue INREBIC and initiate parenteral thiamine.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
N/A	

AVAILABLE DOSAGE FORMS:
Inrebic CAPS 100MG

REFERENCES

1. Inrebic® capsules [prescribing information]. Summit, NJ: Celgene; October 2022.
2. 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- randomized, phase 2, multicenter study. Lancet Haematol 2017;4(7):e317-e324
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8. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012; 30:4098.
9. NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms (Version 3.2019). Retrieved 9 October 2019, from https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf
10. National Comprehensive Cancer Network. 2023. Myeloproliferative Neoplasms (Version 3.2022). [online] Available at: < mpn.pdf (nccn.org) > [Accessed 2 April 2023].

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/Discontinuation Other Special Considerations References	Q2 2023
Q2 2022 Established tracking in new format	Historical changes on file