Fedratinib (INREBIC)
Criteria for Use
June 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive fedratinib.

- ☐ Unable to comply with recommended laboratory monitoring.
- ☐ History of recurrent Wernicke's encephalopathy.
- ☐ Uncontrolled alcohol use disorder.
- ☐ Absolute neutrophil count less than 1.0×10^9/L.
- ☐ Platelet count less than 50×10^9/L.
- ☐ Severe liver impairment (Child-Pugh Class C).
- ☐ Total bilirubin ≥ 3.0 x ULN.
- ☐ AST or ALT ≥ 2.5 x ULN.
- ☐ History of chronic liver disease, unless a hepatologist documents that fedratinib may be initiated safely.
- ☐ Serum amylase or lipase > 1.5 x ULN.
- ☐ Active, uncontrolled systemic or localized infection.
- ☐ Untreated latent or active tuberculosis infection.
- ☐ Active hepatitis A.
- ☐ Hepatitis B surface antigen (HBsAg)-positive and not on antiviral prophylaxis.[1] Fedratinib may be initiated after starting antiviral prophylaxis.
- ☐ HBsAg-negative but antibody-to-hepatitis-B-core-antigen (anti-HBc)-positive and not on antiviral prophylaxis.[1] Fedratinib may be initiated after starting antiviral prophylaxis.
- ☐ Untreated hepatitis C. Fedratinib may be initiated after starting antiviral treatment or if there is documentation that antiviral therapy is not indicated.
- ☐ Untreated HIV infection or at high risk for HIV infection. Treated, well-controlled, asymptomatic HIV-positive patients can be treated with fedratinib.
- ☐ Concomitant live or live-attenuated vaccines or administration of inactivated, live, or live-attenuated vaccines less than 2 weeks before initiation of fedratinib.
- ☐ Uncontrolled NYHA Class 3 or 4 heart failure, unless a cardiologist documents that fedratinib may be initiated safely (not studied).

- ☐ Strong or moderate CYP3A4 inDUCers (e.g., rifampin).
- ☐ Dual CYP3A4 and CYP2C19 inhibitors (e.g., fluvoxamine).
- ☐ Breastfeeding.

[1] **Antiviral prophylaxis for HBV**: Agents with high genetic barrier to resistance such as entecavir or tenofovir should be used.

Inclusion Criteria

All of the following criteria must be met:

- ☐ Care is provided by a VA / VA Community Care hematologist or locally designated myelofibrosis expert.
- ☐ Goals of care and role of Palliative Care consult have been discussed and documented.
- ☐ Intermediate (INT)-2- or high-risk myelofibrosis,[1] including primary myelofibrosis or secondary myelofibrosis (post-polycythemia vera or post-essential thrombocythemia).
- ☐ Splenomegaly by palpation (at least 5 cm below costal margin) or imaging.
- ☐ ECOG performance status of 0 to 2.
- ☐ Thiamine level within the normal reference range used by local laboratory. If deficient, replete thiamine prior to initiating fedratinib.
- ☐ Completed tuberculosis (TB) test using tuberculin skin test or interferon-gamma release assay [IGRA].
- ☐ Completed hepatitis B screening (at minimum, HBsAg, anti-HBc and anti-HBs).[2]
- ☐ Completed hepatitis C screening.
- ☐ Patient able and willing to have hemoglobin monitored for transfusion requirement.
- ☐ Patient able and willing to have thiamine levels monitored.
- ☐ **Ruxolitinib** is medically inadvisable,[3] not tolerated despite dosage modifications, or not adequate.[4]
- ☐ For patients on ruxolitinib: Ruxolitinib has been tapered and discontinued before initiation of fedratinib.
- ☐ Fedratinib is prescribed at the FDA-approved dose for myelofibrosis, modified as recommended for CYP3A4 inhibitor drug interactions, severe renal impairment (CrCl 15–29 mL/min), Grade 3 or 4 toxicities, and treatment-emergent transfusion dependence.
- ☐ Patient will receive antiemetics (e.g., ondansetron) to prevent or treat fedratinib-induced nausea or vomiting.
- ☐ For women of childbearing age and men who partner with women of childbearing potential: Provided counseling on use of effective contraception to prevent pregnancy and on risks and benefits of treatment.

[1] As determined on initial diagnosis by modified International Prognostic Scoring System (IPSS) or on risk assessment by Dynamic International Prognostic Scoring System (DIPSS)-Plus or DIPSS during / despite ruxolitinib therapy. For further details on scoring systems, refer to NCCN Guidelines for Myeloproliferative Neoplasms at https://www.nccn.org .

[2] Anti-HBs may help to identify patients who require initial or booster vaccination (anti-HBs titers >= 10 IU/L are generally considered protective) or HBsAg-negative patients without past vaccination who have occult HBV from past infection (anti-HBs positive and lost anti-HBc).

[3] Reasons for ruxolitinib being **medically inadvisable** include (and are not limited to) (1) absolute neutrophil count persists below 0.75 x 10^9/L (however, to give fedratinib, neutropenia should be grade ≤ 2 and platelet count ≥ 50 x 10^9/L); and (2) concomitant fluconazole is required at doses greater than 200 mg daily.

[4] **Not adequate** refers to NO spleen size reduction or myelofibrosis symptom improvement, or worsening of spleen size or myelofibrosis symptoms, after 6 months of ruxolitinib therapy, or loss of initial response.

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