INREBIC®
(fedratinib) capsules
100mg

Bristol Myers Squibb®
Access Support®
Your patient. Our commitment.

A REFERENCE GUIDE TO

Reimbursement and Coding INREBIC® (fedratinib) capsules

To view authorized distributors/specialty pharmacies for INREBIC, please click here or visit BMSAccessSupport.com.

Please see Important Safety Information on pages 8–10 and US full Prescribing Information, including **Boxed WARNING**.

Indication

INREBIC® (fedratinib) is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).

Select Important Safety Information: **Boxed WARNING**

WARNING: 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. Monitor until symptoms resolve or improve and thiamine levels normalize.

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For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday–Friday, or visit www.BMSAccessSupport.com.

Bristol Myers Squibb Is Committed to Helping Support Access

This brochure is designed to help appropriate patients get access to our medications by providing helpful reimbursement information for healthcare offices. Healthcare benefits vary significantly; therefore, it is important that healthcare provider offices verify each patient's insurance coverage prior to initiating therapy.

Table of Contents

Healthcare providers should code healthcare claims based upon the service that is rendered, the patient's medical record, the coding requirements of each health insurer, and the best coding practices. The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

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National Drug Code (NDC) Information and Storage for INREBIC®

NDCs for INREBIC[1]

Bottles of 120 capsules

10-digit NDC
59572-720-12

11-digit NDC*
59572-0720-12

*The red zero converts the 10-digit NDC to the 11-digit NDC. Some payers may require each NDC to be listed on the claim. Payer requirements regarding the use of NDCs may vary. Electronic data exchange generally requires use of the 11-digit NDC.

Storage[1]

INREBIC 100 mg capsules are supplied in bottles of 120 count each.

Store below 86 °F (30 °C).

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ICD-10-CM Codes

ICD-10-CM codes are used to identify a patient's diagnosis. On October 1, 2015, the newest version of these codes, ICD-10-CM, was implemented throughout the United States. This version replaces the previous version, ICD-9-CM.[2]

- The ICD-10-CM diagnosis codes contain **categories**, **subcategories**, and **codes**. Characters for categories, subcategories, and codes may be letters or numerals.
- **All categories** are 3 characters
- **Subcategories** are either 4 or 5 characters
- **Codes** may be 3, 4, 5, 6, or 7 characters

The ICD-10-CM codes for the labeled indications for INREBIC® (fedratinib) capsules are provided on the following pages by Bristol Myers Squibb and should be verified with the payer. Some health plan and Medicare insurers may specify which codes are covered under their policies. Please code to the level of specificity documented in the medical record. For additional coding questions, call BMS Access Support® at **1-800-861-0048,** 8 AM to 8 PM ET, Monday–Friday, or visit **www.BMSAccessSupport.com**.

ICD-10-CM Codes for INREBIC® (fedratinib): Myelofibrosis (MF)

ICD-10-CM Codes for INREBIC[3]	
D47.4	Osteomyelofibrosis
D75.81	Myelofibrosis

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Dosage and Administration for INREBIC® (fedratinib)[1]

IMPORTANT ADMINISTRATION INFORMATION

Conduct baseline testing of thiamine (Vitamin B1) levels prior to initiation of INREBIC.

Recommended Dosage[1]

- The recommended dosage of INREBIC is 400 mg taken orally once daily for patients with a baseline platelet count of greater than or equal to 50 x 10^9/L

400 mg orally once daily

- INREBIC may be taken with or without food. Administration with a high-fat meal may reduce the incidence of nausea and vomiting
- Modify the dose for patients using concomitant strong CYP3A4 inhibitors, and in patients with severe renal impairment (creatinine clearance (CL_{cr}) 15 mL/min to 29 mL/min)
- If a dose of INREBIC is missed, the next scheduled dose should be taken the following day
- Patients who are on treatment with ruxolitinib before the initiation of INREBIC must taper and discontinue according to the ruxolitinib prescribing information

Monitoring for Safety

Obtain the following blood tests prior to starting treatment with INREBIC, periodically during treatment, and as clinically indicated:

- Thiamine (Vitamin B1) level
- Complete blood count with platelets
- Creatinine and BUN
- Hepatic panel
- Amylase and lipase

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Dosage and Administration for INREBIC® (fedratinib)[1] (cont.)

Dose Modifications With Concomitant Use of Strong CYP3A4 Inhibitors

Reduce INREBIC dose when administering with strong CYP3A4 inhibitors to 200 mg once daily.
In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, INREBIC dosage should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg once daily thereafter as tolerated.

Dose Modifications for Severe Renal Impairment

Reduce INREBIC dose to 200 mg once daily in patients with severe renal impairment (creatinine clearance (CL_{cr}) 15 mL/min to 29 mL/min as estimated by Cockcroft-Gault (C-G) equation.

Dose Modifications for Adverse Reactions

Modify dose for hematologic and non-hematologic adverse reactions per Table 1 and Table 2. Discontinue INREBIC in patients unable to tolerate a dose of 200 mg daily. See Warnings and Precautions for other mitigating strategies.

Table 1: Dose Modifications for Hematologic Adverse Reactions

Hematologic Adverse Reactions	Dose Reduction
Grade 4 Thrombocytopenia or Grade 3 Thrombocytopenia with active bleeding	Interrupt dose until resolved to Grade 2 or lower or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 4 Neutropenia	Interrupt dose until resolved to Grade 2 or lower or baseline. Restart dose at 100 mg daily below the last given dose.

Consider dose reductions for patients who become transfusion-dependent during treatment with INREBIC.

Table 2: Dose Reductions for Non-hematologic Adverse Reactions

Non-hematologic Adverse Reactions	Dose Reduction
Grade 3 or higher Nausea, Vomiting, or Diarrhea not responding to supportive measures within 48 hours	Interrupt dose until resolved to Grade 1 or lower or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 3 or higher ALT, AST, or Bilirubin	Interrupt dose until resolved to Grade 1 or lower or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST, and bilirubin (total and direct) more frequently following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment with INREBIC.
Grade 3 or higher Other Non-hematologic Toxicities	Interrupt dose until resolved to Grade 1 or lower or baseline. Restart dose at 100 mg daily below the last given dose.

Management of Thiamine Levels and Wernicke's Encephalopathy (WE)

Assess thiamine levels and nutritional status prior to starting INREBIC and periodically during treatment and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation and during treatment if thiamine levels are low. If Wernicke's encephalopathy is suspected, immediately discontinue treatment with INREBIC and initiate parenteral thiamine treatment. Monitor until symptoms resolve or improve and thiamine levels normalize.

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Important Safety Information for INREBIC® (fedratinib)

WARNING: 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. Monitor until symptoms resolve or improve and thiamine levels normalize.

WARNINGS AND PRECAUTIONS

Encephalopathy, including Wernicke's: Serious and fatal encephalopathy, including Wernicke's encephalopathy, has occurred in INREBIC-treated patients. Serious cases were reported in 1.3% (8/608) of patients treated with INREBIC in clinical trials and 0.16% (1/608) of cases were fatal.

Wernicke's encephalopathy is a neurologic emergency resulting from thiamine (Vitamin B1) deficiency. Signs and symptoms of Wernicke's encephalopathy may include ataxia, mental status changes, and ophthalmoplegia (e.g., nystagmus, diplopia). Any change in mental status, confusion, or memory impairment should raise concern for potential encephalopathy, including Wernicke's, and prompt a full evaluation including a neurologic examination, assessment of thiamine levels, and imaging. 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. Monitor until symptoms resolve or improve and thiamine levels normalize.

Anemia: New or worsening Grade 3 anemia occurred in 34% of INREBIC-treated patients. The median time to onset of the first Grade 3 anemia was approximately 2 months, with 75% of cases occurring within 3 months. Mean hemoglobin levels reached a nadir after 12 to 16 weeks with partial recovery and stabilization after 16 weeks. Red blood cell transfusions were received by 51% of INREBIC-treated patients and permanent discontinuation of INREBIC due to anemia occurred in 1% of patients. Consider dose reduction for patients who become red blood cell transfusion dependent.

Thrombocytopenia: New or worsening Grade 3 or higher thrombocytopenia during the randomized treatment period occurred in 12% of INREBIC-treated patients. The median time to onset of the first Grade 3 thrombocytopenia was approximately 1 month, with 75% of cases occurring within 4 months. Platelet transfusions were received by 3.1% of INREBIC-treated patients. Permanent discontinuation of treatment due to thrombocytopenia and bleeding that required clinical intervention both occurred in 2.1% of INREBIC-treated patients. Obtain a complete blood count (CBC) at baseline, periodically during treatment, and as clinically indicated. For Grade 3 thrombocytopenia with active bleeding or Grade 4 thrombocytopenia, interrupt INREBIC until resolved to Grade 2 or lower or to baseline. Restart dose at 100 mg daily below the last given dose and monitor platelets as clinically indicated.

Gastrointestinal Toxicity: Gastrointestinal toxicities are the most frequent adverse reactions in INREBIC-treated patients. During the randomized treatment period, diarrhea occurred in 66% of patients, nausea in 62% of patients, and vomiting in 39% of patients. Grade 3 diarrhea occurred in 5% and Grade 3 vomiting in 3.1%. The median time to onset of any grade nausea, vomiting, and diarrhea was 1 day, with 75% of cases occurring within 2 weeks of treatment. Consider providing appropriate prophylactic antiemetic therapy (e.g., 5-HT3 receptor antagonists) during INREBIC treatment. Treat diarrhea with antidiarrheal medications promptly at the first onset of symptoms. Grade 3 or higher nausea, vomiting, or diarrhea not responsive to supportive measures within 48 hours, interrupt INREBIC until resolved to Grade 1 or lower or to baseline. Restart dose at 100 mg daily below the last given dose. Monitor thiamine levels and replete as needed.

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Important Safety Information for INREBIC® (fedratinib) (cont.)

Hepatic Toxicity: Elevations of ALT and AST (all grades) during the randomized treatment period occurred in 43% and 40%, respectively, with Grade 3 or 4 in 1% and 0%, respectively, of INREBIC-treated patients. The median time to onset of any grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 3 months. Monitor hepatic function at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher ALT and/or AST elevations (greater than 5 × ULN), interrupt INREBIC dose until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose. If reoccurrence of a Grade 3 or higher elevation of ALT/AST, discontinue treatment with INREBIC.

Amylase and Lipase Elevation: Grade 3 or higher amylase and/or lipase elevations developed in 2% and 10% of INREBIC-treated patients, respectively. The median time to onset of any grade amylase or lipase elevation was 15 days, with 75% of cases occurring within 1 month of starting treatment. One patient developed pancreatitis in the fedratinib clinical development program (n=608) and pancreatitis resolved with treatment discontinuation. Monitor amylase and lipase at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher amylase and/or lipase elevations, interrupt INREBIC until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose.

Major Adverse Cardiac Events (MACE): Another JAK inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke in patients with rheumatoid arthritis (compared to those treated with TNF blockers), a condition for which INREBIC is not indicated. Consider the benefits and risks of the individual patients prior to initiating or continuing therapy with INREBIC, particularly in patients who are current or past smokers, or have other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and what to do if they occur.

Thrombosis: Another JAK inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis in patients with rheumatoid arthritis (compared to those treated with TNF blockers), a condition for which INREBIC is not indicated. In patients with MF treated with INREBIC in clinical trials, the rates of thromboembolic events were similar in INREBIC and placebo treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Secondary Malignancies: Another JAK inhibitor has increased the risk of lymphoma and other malignancies excluding nonmelanoma skin cancer (NMSC) in patients with rheumatoid arthritis, a condition for which INREBIC is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with INREBIC, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

ADVERSE REACTIONS

The most common adverse reactions for INREBIC treated vs. placebo were diarrhea (66% vs. 16%), nausea (62% vs. 15%), anemia (40% vs. 14%), and vomiting (39% vs. 5%). Dosage interruptions due to an adverse reaction during the randomized treatment period occurred in 21% of patients who received INREBIC. Adverse reactions requiring dosage interruption in >3% of patients who received INREBIC included diarrhea and nausea. Dosage reductions due to an adverse reaction during the randomized treatment period occurred in 19% of patients who received INREBIC. Adverse reactions requiring dosage reduction in >2% of patients who received INREBIC included anemia (6%), diarrhea (3%), vomiting (3%), and thrombocytopenia (2%).

DRUG INTERACTIONS

Coadministration of INREBIC with a strong CYP3A4 inhibitor increases fedratinib exposure. Increased exposure may increase the risk of adverse reactions. Consider alternative therapies that do not strongly inhibit CYP3A4 activity. Alternatively, reduce

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Important Safety Information for INREBIC® (fedratinib) (cont.)

the dose of INREBIC when administering with a strong CYP3A4 inhibitor. Avoid INREBIC with strong and moderate CYP3A4 inducers. Coadministration of INREBIC with a dual CYP3A4 and CYP2C19 inhibitor increases fedratinib exposure. Increased exposure may increase the risk of adverse reactions. Due to potential increase of exposure, patients taking concomitant dual CYP3A4 and CYP2C19 inhibitors require more intensive safety monitoring and, if necessary, dose modifications of INREBIC based on adverse reactions. Coadministration of INREBIC with drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates increases the concentrations of these drugs, which may increase the risk of adverse reactions of these drugs. Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when coadministered with INREBIC. Coadministration of INREBIC with drugs that are renally excreted via organic cation transporter (OCT2) and multidrug and toxin extrusion (MATE)1/2-K can decrease renal clearance of those drugs. Monitor for adverse reactions and consider dose modifications for drugs that are renally excreted via OCT2 or MATE1/2-K (e.g., metformin) as necessary when coadministered with INREBIC.

PREGNANCY/LACTATION

Consider the benefits and risks of INREBIC for the mother and possible risks to the fetus when prescribing INREBIC to a pregnant woman. Due to the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with INREBIC, and for at least 1 month after the last dose.

RENAL IMPAIRMENT

Reduce INREBIC dose when administered to patients with severe renal impairment. No modification of the starting dose is recommended for patients with mild to moderate renal impairment. Due to potential increase of exposure, patients with preexisting moderate renal impairment require more intensive safety monitoring, and if necessary, dose modifications based on adverse reactions.

HEPATIC IMPAIRMENT

Avoid use of INREBIC in patients with severe hepatic impairment.

References

1. INREBIC® (fedratinib). Prescribing Information. Bristol-Myers Squibb Company.
2. eHealth University, Centers for Medicare & Medicaid Services. The ICD-10- transition: an introduction. Updated August 2014. Accessed December 15, 2021. https://www.cms.gov/Medicare/Coding/ICD10/Downloads/ICD10Introduction20140819.pdf
3. Centers for Medicare & Medicaid Services. ICD-10-CM tabular list of diseases and injuries. Accessed May 6, 2021. https://www.cms.gov/medicare/icd-10/2021-icd-10-cm

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Scheduling a meeting with a BMS Access and Reimbursement Manager on the BMS Access Support website

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