NOW APPROVED AND AVAILABLE

INTRODUCING **INREBIC®** (fedratinib) capsules

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).

August 2019

Celgene Corporation is pleased to announce that INREBIC® is now approved and available for adult patients with intermediate-2 or high-risk primary or secondary myelofibrosis.

INREBIC® EFFICACY

INREBIC® 400 mg once daily for the treatment of myelofibrosis

Study design: primary or secondary MF	• Double-blind, placebo-controlled trial (JAKARTA) in 289 patients randomized to receive either INREBIC® 500 mg (n=97), INREBIC® 400 mg (n=96), or placebo (n=96) once daily for at least 6 cycles • Intermediate-2 and high-risk International Prognostic Scoring System (IPSS) risk status • Platelet counts ≥50 × 10^9/L • The primary end point was the proportion of patients with ≥35% reduction from baseline in spleen volume at the end of cycle 6 as measured by MRI or CT with a follow-up scan 4 weeks later • A secondary end point was the proportion of patients with a ≥50% reduction in Total Symptom Score (TSS) from baseline to the end of cycle 6 as measured by the modified MFSAF v2.0 diary
Efficacy results: Spleen and symptom reduction	• 37% of patients receiving INREBIC® 400 mg experienced spleen volume reduction ≥35% at the end of cycle 6 with a follow-up scan 4 weeks later, vs 1% of patients receiving placebo • 40% of patients receiving INREBIC® 400 mg experienced ≥50% reduction in TSS at the end of cycle 6, vs 9% of patients receiving placebo

SELECTED IMPORTANT SAFETY INFORMATION

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.

Abbreviations: CT, computed tomography; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging.

Please see Important Safety Information on pages 6-7 and full Prescribing Information, including Boxed WARNING.

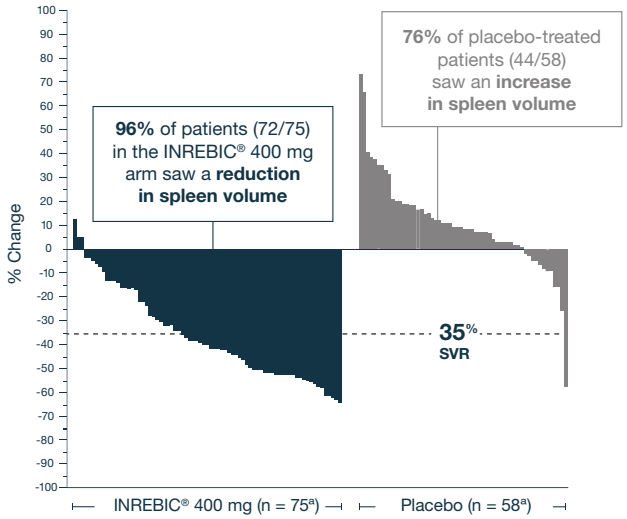
INREBIC®
(fedratinib) capsules
100mg

INREBIC® (fedratinib) EFFICACY (CONT'D)

Percent of Patients Achieving ≥35% Reduction from Baseline in Spleen Volume at the End of Cycle 6

Spleen Response by MRI/CT at the End of Cycle 6 With a Follow-up Scan 4 Weeks Later	INREBIC® 400 mg N=96 n (%)	Placebo N=96 n (%)
Number (%) of Patients with Spleen Volume Reduction by ≥35%	35 (37%)	1 (1%)
P-value	*P*<0.0001	

Percentage Change in Spleen Volume at the End of Cycle 6

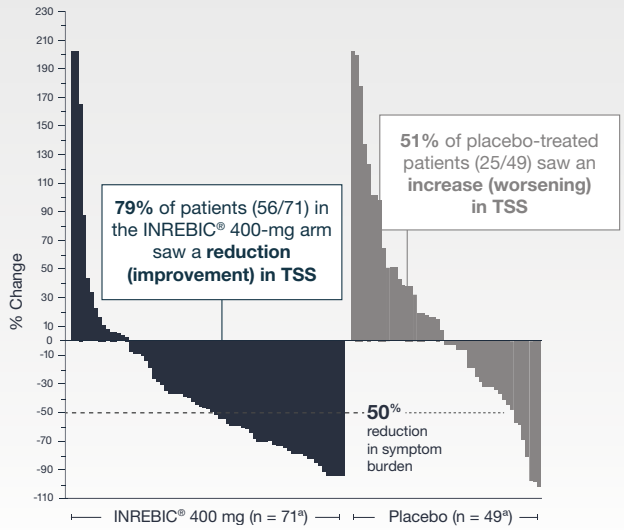


[a]Patients with available percentage change in spleen volume at end of cycle 6.

Improvement in Total Symptom Score (TSS) in Patients with Myelofibrosis

Symptom Response at the End of Cycle 6	INREBIC® 400 mg N=89 n (%)	Placebo N=81 n (%)
Number (%) of Patients With ≥50% Reduction (Improvement) in TSS	36 (40%)	7 (9%)
P-value	*P*<0.0001	

Percentage Change in TSS at the End of Cycle 6



[a]Patients with available percentage change in TSS at end of cycle 6.

SELECTED IMPORTANT SAFETY INFORMATION (cont'd)

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.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; TSS, Total Symptom Score.

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INREBIC® (fedratinib) capsules 100mg

Encephalopathy, including Wernicke's encephalopathy (WE), with INREBIC® (fedratinib)

- 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 WE may include ataxia, mental status changes, and ophthalmoplegia (eg, nystagmus, diplopia)
- Any change in mental status, confusion, or memory impairment should raise concern for potential encephalopathy, including WE, 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

Dosage and administration

Considerations prior to initiation of treatment

- Thiamine levels and nutritional status should be assessed prior to initiation of INREBIC®. INREBIC® should not be started in patients with thiamine deficiency. Thiamine should be repleted prior to treatment initiation and during treatment if thiamine levels are low
- In addition to thiamine levels, blood tests that should be obtained prior to starting INREBIC®, periodically during treatment, and as clinically indicated include a complete blood count with platelets, creatinine, BUN, hepatic panel, amylase, and lipase
- Patients who are on treatment with ruxolitinib before the initiation of INREBIC® must taper and discontinue according to the ruxolitinib prescribing information

Recommended dosage

- The recommended dose of INREBIC® is 400 mg taken orally once daily for patients with a baseline platelet count of ≥50 × 10^9/L
- Reduce the INREBIC® dose to 200 mg for patients using concomitant strong CYP3A4 inhibitors, and in patients with severe renal impairment (CL_{cr} 15 mL/min to 29 mL/min)
- INREBIC® may be taken with or without food. Administration with a high-fat meal may reduce the incidence of nausea and vomiting

Missed dose

- If a dose of INREBIC® is missed, the next scheduled dose should be taken the following day

There are no contraindications to INREBIC®.

SELECTED IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Encephalopathy, including Wernicke's (cont'd): 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.

Abbreviations: BUN, blood urea nitrogen; CL_{cr}, creatinine clearance.

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INREBIC®
(fedratinib) capsules
100mg

ORDERING INFORMATION

National Drug Codes			
10-Digit NDC	**11-Digit NDC[a]**	**Dosage Strength**	**Description**
59572-720-12	59572-0720-12	100 mg/capsule	Bottle of 120 reddish brown, opaque size 0 capsules, printed with “FEDR 100 mg” in white ink

[a]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.

Commonly used diagnosis codes*

ICD-9

- 238.76 (Myelofibrosis with Myeloid Metaplasia)
- 289.83 (Myelofibrosis)

ICD-10

- D47.4 (Osteomyelofibrosis)
- D75.81 (Myelofibrosis)

*This list may not be all-inclusive.

Additional Product Information

HOW SUPPLIED

INREBIC® (fedratinib) 100 mg capsules are supplied in bottles of 120 count each

STORAGE

- Store below 86°F (30°C)

SELECTED IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

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 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 occurred due to anemia in 1% of patients. Consider dose reduction for patients who become red blood cell transfusion dependent.

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; NDC, National Drug Code.

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CELGENE PATIENT SUPPORT®

A single source for access support

Celgene Patient Support® provides

- A single Specialist assigned to help patients in your geographic area
- Assistance with understanding patient insurance coverage for INREBIC® (fedratinib)
- Information about financial assistance for INREBIC®

Financial assistance

Depending on a patient's insurance situation, there are programs and organizations that may help pay for INREBIC®.

Celgene Commercial Co-pay Program

- Reduces co-pay responsibility to $25 for INREBIC® (subject to annual benefit limit) for eligible patients with commercial or private insurance (including healthcare exchanges)*

Celgene Patient Assistance Program (PAP)

For qualified patients who are uninsured or underinsured, INREBIC® may be available at no cost†

Independent Third-Party Organizations

For patients who are unable to afford their medication (including patients with Medicare, Medicaid, or other government-sponsored insurance), independent third-party organizations may be able to help‡

There are 3 simple ways to enroll in Celgene Patient Support®

Enroll online at
www.celgenepatientsupport.com

Call us at 1-800-931-8691
Monday - Friday, 8 AM - 8 PM ET
(*translation services available*)

E-mail or fax a completed enrollment form to
patientsupport@celgene.com or fax 1-800-822-2496

*Eligibility requirements and restrictions apply. Please see full Terms and Conditions on the Celgene Patient Support® website.

†Patients must meet specified financial and insurance eligibility requirements to qualify for assistance. Please see full Eligibility Requirements on the Celgene Patient Support® website.

‡Financial and medical eligibility requirements vary by organization.

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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).

IMPORTANT SAFETY INFORMATION

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 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 occurred due to anemia in 1% of patients. Consider dose reduction for patients who become red blood cell transfusion dependent.

Thrombocytopenia: New or worsening Grade ≥3 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% 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 less than or equal to Grade 2 or 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 patient and vomiting in 39% of patients. Grade 3 diarrhea 5% and vomiting 3.1% occurred. 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 anti-emetic therapy (e.g., 5-HT3 receptor antagonists) during INREBIC treatment. Treat diarrhea with anti-diarrheal 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 less or 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 (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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 re-occurrence of a Grade 3 or higher elevation of ALT/AST, discontinue treatment with INREBIC.

Amylase and Lipase Elevation: Grade 3 or higher amylase 2% and/or lipase 10% elevations developed in INREBIC-treated patients. 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.

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 the dose of INREBIC when administering with a strong CYP3A4 inhibitor. Avoid INREBIC with strong and moderate CYP3A4 inducers. Avoid INREBIC with dual CYP3A4 and CYP2C19 inhibitor. Coadministration of INREBIC with drugs that are CYP3A4 substrates, CYP2C19 substrates, 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.

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.

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Celgene

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