INREBIC®
(fedratinib) capsules
100mg

Clinical Overview of INREBIC®

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including Boxed WARNING, inside pocket.

INREBIC® was studied as initial therapy in patients with intermediate-2 or high-risk primary or secondary myelofibrosis (MF)[1]

Study design

- JAKARTA was a double-blind, placebo-controlled, phase-3 study of 289 patients randomized to receive INREBIC® 500 mg (n=97), 400 mg (n=96), or placebo (n=96) once daily for at least 6 cycles

Primary endpoint

- The proportion of patients achieving ≥35% spleen volume reduction (SVR) at the end of cycle 6 as measured by magnetic resonance imaging (MRI) or computed tomography (CT) with a scan 4 weeks later was 37% in the INREBIC® 400-mg arm (n=35/96) vs 1% in the placebo arm (n=1/96) (*P*<0.0001)

Secondary endpoint

- The proportion of patients achieving ≥50% reduction in Total Symptom Score (TSS) at the end of cycle 6 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary was 40% in the INREBIC® 400-mg arm (n=36/89) vs 9% in the placebo arm (n=7/81) (*P*<0.0001)*

Adverse reactions

- The most common adverse reactions (all grades) for INREBIC®-treated vs placebo patients were diarrhea (66% vs 16%), nausea (62% vs 15%), anemia (40% vs 14%), and vomiting (39% vs 5%)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)† recommend fedratinib as initial therapy (category 2B) for[2]

- Patients with intermediate-2 or high-risk MF
- AND platelets ≥50 x 10^9/L
- AND who are transplant ineligible

*The modified MFSAF included 6 key MF-associated symptoms: night sweats, itching, abdominal discomfort, early satiety, pain under the ribs on the left side, and bone or muscle pain. The symptoms were measured on a scale of 0 (absent) to 10 (worst imaginable).

†NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IMPORTANT SAFETY INFORMATION (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.

INREBIC® was also studied in patients previously treated with ruxolitinib[3]

Limitations: JAKARTA2, a phase-2, single-arm open-label study, was prematurely terminated, which impacts the interpretability of the data. No conclusions regarding the benefits or risks of fedratinib in patients who are resistant or intolerant to ruxolitinib can be established based on this study. These data are not included in the Prescribing Information

Study overview

- JAKARTA2 was a single-arm, open-label, phase-2 study in 97 primary or secondary MF patients who were resistant or intolerant to ruxolitinib per investigator assessment
- Median exposure to ruxolitinib prior to enrollment in study was 10.7 months. Median exposure to INREBIC® during enrollment in study was 24 weeks (range 0.7-79.4 weeks)
- Post hoc analyses of spleen volume in the intent-to-treat (ITT) population and of TSS were conducted. Only patients who were confirmed responders at the end of cycle 6 were included; patients missing spleen volume assessments at the end of cycle 6 were considered nonresponders
- The primary endpoint was the proportion of patients achieving ≥35% SVR at the end of cycle 6 as measured by MRI or CT. The percentage of patients in the ITT population with SVR ≥35% at the end of cycle 6 was 30.9% (n=30/97)
- Secondary endpoints included the proportion of patients achieving ≥50% reduction in TSS at the end of cycle 6 as measured by the modified MFSAF v2.0 diary.* The percentage of patients achieving ≥50% reduction in TSS at the end of cycle 6 was 26.7% (n=24/90)‡
- The most common hematologic adverse reactions (all grades) during the on-treatment period were anemia (99%) and thrombocytopenia (70.1%). The most common nonhematologic adverse reactions (all grades) occurring in ≥10% of patients were diarrhea (61.9%), nausea (55.7%), and vomiting (41.2%)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)† include fedratinib (category 2A) for[2]

- Patients with intermediate-2 or high-risk MF, previously treated with ruxolitinib with no response or loss of response
- AND platelets ≥50 x 10^9/L
- AND who are transplant ineligible

‡Includes patients with an evaluable baseline and ≥1 post-baseline assessment of TSS.

IMPORTANT SAFETY INFORMATION (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.

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IMPORTANT SAFETY INFORMATION (cont'd)

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% 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 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 patients, 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.

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.

Please see full Prescribing Information, including Boxed WARNING, in pocket.

REFERENCES: 1. INREBIC® [package insert]. Summit, NJ: Celgene Corporation; 2019. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 18, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** Data on file.

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