# Bristol Myers Squibb Receives European Commission Approval for Inrebic® (fedratinib) for Adult Patients with Newly Diagnosed and Previously Treated Myelofibrosis

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***Inrebic, a once-daily, oral therapy, is the first new treatment option approved in Europe for myelofibrosis in nearly a decade***

***Inrebic demonstrated clinically meaningful spleen and symptom response in myelofibrosis patients where treatment with ruxolitinib has failed, who are intolerant to ruxolitinib or who are JAK inhibitor naïve, based on results from JAKARTA and JAKARTA2 studies***

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced that the European Commission (EC) has granted full Marketing Authorization for *Inrebic*® (fedratinib) for the treatment of disease-related splenomegaly (enlarged spleen) or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis, who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib. *Inrebic* is the first, once-daily oral therapy to significantly reduce spleen volume and symptom burden for patients with myelofibrosis where treatment with ruxolitinib has failed, who are intolerant to ruxolitinib or who are JAK inhibitor naïve. The centralized Marketing Authorization approves use of *Inrebic* in all European Union (EU) member states, as well as Norway, Iceland and Liechtenstein.* *Inrebic* was granted orphan drug designation in the United States and is also approved in the United States and Canada. [1,2]

“Myelofibrosis is a serious and often debilitating bone marrow disorder for which there has only been one approved treatment option for nearly a decade,” said Claire Harrison, M.D., FRCP, FRCPath, JAKARTA and JAKARTA2 study investigator and professor of hematology at Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom. “*Inrebic* showed clinically meaningful reductions in spleen volume and symptoms in patients who progressed on ruxolitinib or who are JAK inhibitor naïve. Approximately one out of every 100,000 people in the EU will be diagnosed with myelofibrosis each year, and today’s approval provides an important new option for patients who have remained in urgent need of new therapies.”

The EC approval of *Inrebic* was based on results from the JAKARTA and JAKARTA2 studies, which included patients from 14 countries in the EU. The pivotal JAKARTA study evaluated the efficacy of once-daily oral doses of *Inrebic* compared with placebo in 289 patients with intermediate-2 or high-risk primary or secondary myelofibrosis with splenomegaly. The JAKARTA2 study evaluated the efficacy of once-daily oral doses of *Inrebic* in 97 patients with intermediate or high-risk primary or secondary myelofibrosis with splenomegaly previously treated with ruxolitinib.[3] In the clinical development program of *Inrebic*, which included 608 patients, serious and fatal cases of encephalopathy, including Wernicke's, 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.[1]

"With today's EC approval of *Inrebic*, patients with myelofibrosis throughout Europe will now have a critical new option for a rare bone marrow disorder that's seen little progress in several years," said Diane McDowell, M.D., vice president, Hematology Global Medical Affairs, Bristol Myers Squibb. "We're committed to improving on standards of care for patients living with hard-to-treat blood diseases and are working collaboratively with European member states to make *Inrebic* available to patients as quickly as possible."

**Centralized Marketing Authorization does not include approval in Great Britain (England, Scotland and Wales).*

## About JAKARTA and JAKARTA2

The *Inrebic* development program consisted of multiple studies (including JAKARTA and JAKARTA2) in 608 patients who received more than one dose (ranging from 30 mg to 800 mg), of whom 459 had myelofibrosis, including 97 previously treated with ruxolitinib.[3] JAKARTA was a pivotal Phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy of once-daily oral doses of *Inrebic*compared with placebo in patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with splenomegaly and a platelet count of ≥50 x $10^9$/L who were previously untreated with a JAK inhibitor. The study included 289 patients randomized to receive either *Inrebic*500 mg (n=97) or 400 mg (n=96) or placebo (n=96) across 94 sites in 24 countries.[1] JAKARTA2 was a Phase 2, open-label, single arm study of *Inrebic* in myelofibrosis patients previously treated with ruxolitinib with a diagnosis of intermediate-1 with symptoms, intermediate-2 or high-risk myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis with splenomegaly and platelet count ≥50 x

$10^9$/L. The study included 97 patients who started *Inrebic* at 400 mg once daily across 10 countries.[3]

The primary endpoint of JAKARTA and JAKARTA2 was spleen response rate, defined as the proportion of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume at the end of cycle 6 as measured by magnetic resonance imaging (MRI) or computerized tomography (CT) with a follow-up scan 4 weeks later in the JAKARTA study. Secondary endpoints of the studies included symptom response rate, defined as the proportion of patients with a 50% or greater reduction in Total Symptom Score when assessed from baseline to the end of cycle 6 as measured by the modified Myelofibrosis Symptoms Assessment Form (MFSAF) v2.0 diary2 (night sweats, itching, abdominal discomfort, early satiety, pain under ribs on left side, bone or muscle pain).[1,3]

## About Myelofibrosis

Myelofibrosis is a serious and rare bone marrow disorder that disrupts the body's normal production of blood cells. 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.[4] Myelofibrosis is classified as a myeloproliferative neoplasm, a group of rare blood cancers that are derived from blood-forming stem cells.[5] In the EU, approximately 1 of every 100,000 people will be diagnosed with myelofibrosis each year.[6] Both men and women are affected, and while the disease can affect people of all ages, the median age at diagnosis ranges from 60 to 67 years.[7,8] Median survival after ruxolitinib discontinuation is generally poor, ranging from 6 months to 2 years,representing a significant need for alternative treatment options.[9]

## About *Inrebic*

*Inrebic* ® (fedratinib) is an oral kinase inhibitor with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). *Inrebic* is a JAK2-selective inhibitor with higher potency for JAK2 over family members JAK1, JAK3 and TYK2. Abnormal activation of JAK2 is associated with myeloproliferative neoplasms, including myelofibrosis and polycythemia vera. In cell models expressing mutationally active JAK2 or FLT3, *Inrebic* reduced phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibited cell proliferation, and induced apoptotic cell death. In mouse models of JAK2V617F-driven myeloproliferative disease, *Inrebic* blocked phosphorylation of STAT3/5,

increased survival and improved disease-associated symptoms, including reduction of white blood cells, hematocrit, splenomegaly and fibrosis.[1]

## U.S. 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).

## U.S. 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% 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, and Summary of Product Characteristics for INREBIC.**

## Bristol Myers Squibb: Creating a Better Future for People with Cancer

Bristol Myers Squibb is inspired by a single vision—transforming patients' lives through science. The goal of the company's cancer research is to deliver medicines that offer each patient a better, healthier life and to make cure a possibility. Building on a legacy across a broad range of cancers that have changed survival expectations for many, Bristol Myers Squibb researchers are exploring new frontiers in personalized medicine, and through innovative digital platforms, are turning data into insights that sharpen their focus. Deep scientific expertise, cutting-edge capabilities and discovery platforms enable the company to look at cancer from every angle. Cancer can have a relentless grasp on many parts of a patient's life, and Bristol Myers Squibb is committed to taking actions to address all aspects of care, from diagnosis to survivorship. Because as a leader in cancer care, Bristol Myers Squibb is working to empower all people with cancer to have a better future.

## About Bristol Myers Squibb

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube, Facebook and Instagram.

Celgene and Juno Therapeutics are wholly owned subsidiaries of Bristol-Myers Squibb Company. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol Myers Squibb company and Juno Therapeutics, a Bristol Myers Squibb company.

**Bristol Myers Squibb Cautionary Statement Regarding Forward-Looking Statements**

*This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that the outcome of pricing and reimbursement negotiations in individual countries in Europe may delay or limit the commercial potential of Inrebic® (*fedratinib) *for the additional indication described in this release, that continued approval of such product candidate for such additional indication described in this release may be contingent upon verification and description of clinical benefit in confirmatory trials, and whether such product candidate for such additional indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb's business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.*

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