

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212327Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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| PDUFA Goal Date | September 3, 2019 |
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| Reviewer Name(s) | Brad Moriyama, Pharm.D. |
| Team Leader | Elizabeth Everhart, MSN, RN, ACNP |
| Division Director | Cynthia LaCivita, Pharm.D. |
| Review Completion Date | August 7, 2019 |
| Subject | Evaluation of Need for a REMS |
| Established Name | fedratinib |
| Trade Name | Inrebic |
| Name of Applicant | Impact Biomedicines, Inc., a wholly-owned subsidiary of Celgene Corporation |
| Therapeutic Class | kinase inhibitor |
| Formulation(s) | 100 mg capsule |
| Dosing Regimen | 400 mg orally once daily |

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Inrebic (fedratinib) is necessary to ensure the benefits outweigh its risks. Impact Biomedicines, Inc., a wholly-owned subsidiary of Celgene Corporation submitted a New Drug Application (NDA) 212327 for fedratinib with the proposed indication for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis, (b) (4). Upon further review the proposed indication was revised to the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. The serious risks associated with fedratinib include encephalopathy including Wernicke's, anemia and thrombocytopenia, gastrointestinal toxicity, hepatic toxicity, and amylase and lipase elevations. (b) (4)

(b) (4)

DRISK and Division of Hematology Products (DHP) agree that a REMS is not necessary to ensure the benefits of fedratinib outweigh its risks. The efficacy of fedratinib in intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis was supported by the JAKARTA trial in which fedratinib (400 mg group) met the efficacy endpoint of $\geq 35\%$ spleen volume reduction. Wernicke's encephalopathy is an acute neurological emergency that may be fatal if not promptly treated with parenteral thiamine. It is currently unknown if thiamine supplementation will treat fedratinib neurotoxicity. It is also unknown if the strategy of thiamine level monitoring is beneficial as it was not performed during the JAKARTA and JAKARTA2 studies. A required postmarket safety study in patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib will include assessment and management of nausea, diarrhea, vomiting, thiamine deficiency, and encephalopathy. Labeling with a boxed warning and a Medication Guide will be used to communicate the serious risk of encephalopathy including Wernicke's.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Inrebic (fedratinib) is necessary to ensure the benefits outweigh its risks. Impact Biomedicines, Inc., a wholly-owned subsidiary of Celgene Corporation submitted a New Drug Application (NDA) 212327 for fedratinib with the proposed indication for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4).¹ This application is under review in the Division of Hematology Products (DHP). (b) (4)

(b) (4)

2 Background

2.1 PRODUCT INFORMATION

Inrebic (fedratinib), a NME, is a kinase inhibitor, proposed for treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential

thrombocytopenia) myelofibrosis (b) (4). It is active against Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). Fedratinib is supplied as a 100 mg capsule. The proposed dosing regimen is 400 mg orally once daily.^a Fedratinib is not currently approved in any jurisdiction. It was designated an orphan drug.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for fedratinib NDA 212327 relevant to this review:

- 10/24/2007: IND submitted by TargeGen Inc.
- 05/18/2009: Orphan drug designation granted
- 09/21/2010: IND transferred to Sanofi-Aventis U.S. when TargeGen Inc. acquired by Sanofi-Aventis U.S.
- 11/15/2013: FDA placed studies on clinical hold due to issues with Wernicke's encephalopathy and heart failure
- 11/18/2013: Clinical development program terminated
- 11/17/2016: IND transferred to Impact Biomedicines, Inc.
- 08/18/2017: Clinical hold removed after sponsor submitted required documentation to the FDA
- 02/13/2018: Fedratinib IND transferred to Celgene when Impact Biomedicines, Inc. acquired by Celgene
- 05/10/2018: Applicant informed by DHP at pre-NDA meeting that a (b) (4) Medication Guide for fedratinib were needed to mitigate the risk of Wernicke's encephalopathy.
- 01/03/2019: NDA 212327 submission for proposed indication for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocytopenia) myelofibrosis, (b) (4) received.
(b) (4)
- 04/30/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference; the Agency informed the Applicant that (b) (4)
(b) (4)
- 07/23/2019: Email communication to the Applicant informing them that, at this time, the Agency has determined that labeling will be used to communicate the risk of encephalopathy, including Wernicke's, and the need to monitor thiamine levels, via a boxed warning and in warnings and precautions; at this time a CP REMS is not necessary.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

The Philadelphia chromosome-negative myeloproliferative neoplasms include myelofibrosis, polycythemia vera, and essential thrombocythemia.² Myelofibrosis is associated with clonal proliferation of hematopoietic stem cells in the bone marrow, extramedullary hematopoiesis, and leukemic transformation.³ Signs and symptoms of primary myelofibrosis include anemia, hepatosplenomegaly, constitutional symptoms, cachexia, bone pain, splenic infarct, pruritus, thrombosis, and bleeding.⁴ Primary myelofibrosis occurs de novo while secondary myelofibrosis occurs due to transformation of polycythemia vera and essential thrombocythemia. In a study from 2008 to 2010 using data from two large health plans in the United States, the primary myelofibrosis incidence was approximately 1 per 100,000 per year.^{5b} In a study of long term survival and blast transformation rates in patients with polycythemia vera, essential thrombocythemia, and primary myelofibrosis, the median survival for primary myelofibrosis was 5.9 years.^{6c}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Current guidelines from the National Comprehensive Cancer Network (NCCN) for myeloproliferative neoplasms list treatment recommendations for primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis based on risk stratification.² In patients with intermediate-risk 2 or high-risk myelofibrosis who are transplant candidates, allogeneic hematopoietic cell transplant is recommended. In patients who are not transplant candidates and have a platelet count $\leq 50,000$, consideration for enrollment in a clinical trial is recommended. In addition, in patients who are not transplant candidates and have a platelet count $> 50,000$, ruxolitinib or a clinical trial is recommend. Allogeneic hematopoietic cell transplant is the only treatment that may cure myelofibrosis. Ruxolitinib, a kinase inhibitor that inhibits JAK1 and JAK2, was approved by the FDA in 2011 for the treatment of intermediate or high-risk myelofibrosis including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis in adults.⁷ It was also approved for the treatment of polycythemia vera in adults who had an inadequate response to or are intolerant of hydroxyurea and steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years or older. The serious risks associated with ruxolitinib include thrombocytopenia, anemia, neutropenia, risk of infection, symptom exacerbation following interruption or discontinuation, non-melanoma skin cancer, and lipid elevations. Ruxolitinib does not have a boxed warning in its label, and a REMS was not required for approval to ensure the benefits outweigh risks.

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Fifty-one deaths were reported in JAKARTA, with 15 deaths in the fedratinib 400 mg group, 24 deaths in the fedratinib 500 mg group, and 12 deaths in the placebo group.⁸ In addition, 7 deaths were reported on treatment in JAKARTA2. Four deaths were due to disease progression and 3 deaths were due to adverse events (pneumonia, shock, cardiorespiratory arrest).

The serious risks^f associated with fedratinib, which include encephalopathy including Wernicke's, anemia and thrombocytopenia, gastrointestinal toxicity, hepatic toxicity, and amylase and lipase elevation, are summarized in the sections below. At the time of this review the revisions to the label were substantially complete but not yet final. Other changes or additions to the label may occur.

Encephalopathy including Wernicke's

The risk of serious and fatal encephalopathy including Wernicke's will be included in a boxed warning, and section 5 of the label as the first warning and precaution. Encephalopathy including Wernicke's was reported in 8 out of 608 patients in clinical trials. A Division of Neurology Products consult indicated of the 8 potential cases of Wernicke's encephalopathy during the IND phase for fedratinib, 1 case was due to hepatic encephalopathy and 7 cases had a valid diagnosis of Wernicke's encephalopathy.¹¹ The time to onset of Wernicke's encephalopathy in the 7 cases ranged from 44 days to 529 days. There was one fatality related to encephalopathy in a patient with a head and neck cancer with metastases to the brain and an MRI suggestive of encephalopathy.⁸ Thiamine level monitoring was not performed during the JAKARTA and JAKARTA2 studies. The sponsor suggested that preclinical data indicated that fedratinib does not inhibit thiamine transport in the gastrointestinal tract or brain.¹² However, a DHP neuro-oncology consult suggested that inhibition of thiamine function may be a proposed mechanism in the cases of Wernicke's encephalopathy with fedratinib.¹³ The proposed label recommends assessment of thiamine levels and nutritional status prior to starting and during treatment with fedratinib, repletion of thiamine prior to starting treatment, and treatment with parenteral thiamine if encephalopathy is suspected.

A Medication Guide will also be used to inform patients of these risks.

5.1 ANEMIA AND THROMBOCYTOPENIA

Section 5 and section 6 of the labeling indicates that adverse reactions of anemia and thrombocytopenia occurred in 74% and 47% of patients in the fedratinib 400 mg group in JAKARTA, respectively. Grade 3 or greater anemia and thrombocytopenia were reported in 34% and 12% of patients, respectively. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 GASTROINTESTINAL TOXICITY

^f Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Section 5 of the labeling indicates that adverse reactions of nausea, vomiting, and diarrhea occurred in 62%, 39%, and 66% of patients in the fedratinib 400 mg group in JAKARTA, respectively. Grade 3 or greater vomiting and diarrhea were reported in 3.1% and 5% of patients, respectively. The proposed label contains recommendations for the supportive care of nausea and vomiting including consideration of providing prophylactic anti-emetics during fedratinib treatment. The proposed label also contains recommendations for supportive care of diarrhea including antidiarrheal medications at the first onset of symptoms. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 HEPATIC TOXICITY

Section 5 of the labeling indicates that adverse reactions of increased alanine aminotransferase and increased aspartate aminotransferase occurred in 43% and 40% of patients in the fedratinib 400 mg group in JAKARTA, respectively. Grade 3 or greater increased alanine aminotransferase was reported in 1% of patients. The sponsor indicated that 1 case met the criteria for Hy's law in study ARD11936. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4 AMYLASE AND LIPASE ELEVATION

Section 5 and section 6 of the labeling indicates that adverse reactions of increased amylase and increased lipase occurred in 24% and 35% of patients in the fedratinib 400 mg group in JAKARTA, respectively. Grade 3 or greater increased amylase and increased lipase were reported in 2.1% and 10% of patients, respectively. One case of pancreatitis was reported in the clinical development program for fedratinib (1 out of 608 patients). If approved, this risk will be communicated in the warnings and precautions section of the label.

5.5 MONITORING AND DOSAGE REDUCTIONS

In order to mitigate the aforementioned risks, recommendations for monitoring and dose modifications for fedratinib will be addressed in section 2 and in the respective warnings and precautions section of the label. Labeling states to obtain; thiamine (Vitamin B1) level, complete blood count with platelets, creatinine and BUN, hepatic panel and amylase and lipase prior to starting treatment with fedratinib and periodically during treatment, and as clinically indicated.

6 Expected Postmarket Use

If approved, fedratinib will primarily be used in both inpatient and outpatient settings. The likely prescribers will be hematologists and oncologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant proposed a (b) (4) Medication Guide.

(b) (4)

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8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of fedratinib on the basis of the efficacy and safety information currently available. Fedratinib is a kinase inhibitor that is active against JAK2 and FLT3. Upon further review the proposed indication was revised to the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. The efficacy of fedratinib in intermediate-2 or high-risk primary or

secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis was supported by the JAKARTA trial in which fedratinib (400 mg group) met the efficacy endpoint of $\geq 35\%$ spleen volume reduction. The serious risk associated with fedratinib of encephalopathy including Wernicke's will be communicated in a boxed warning, a Medication Guide, and in the warnings and precautions section of the label. The other serious risks including anemia and thrombocytopenia, gastrointestinal toxicity, hepatic toxicity, and amylase and lipase elevation will be communicated in the warnings and precautions section of the label.

Myelofibrosis is a Philadelphia chromosome-negative myeloproliferative neoplasm. It is associated with clonal proliferation of hematopoietic stem cells in the bone marrow, extramedullary hematopoiesis, and leukemic transformation. In a study from 2008 to 2010 using data from two large health plans in the United States, the primary myelofibrosis incidence was approximately 1 per 100,000 per year. Allogeneic hematopoietic cell transplant is the only treatment that may cure myelofibrosis.

DRISK and DHP agree that a (b) (4) REMS is not necessary to ensure that the benefits of fedratinib outweigh its risk. Wernicke's encephalopathy is an acute neurological emergency that may be fatal if not promptly treated with parenteral thiamine.^{14,15,16} It is currently unknown if thiamine supplementation will treat fedratinib neurotoxicity. It is also unknown if the strategy of thiamine level monitoring is beneficial as it was not performed during the JAKARTA and JAKARTA2 studies. The time to onset of Wernicke's encephalopathy did not appear to have a consistent temporal relationship, which may be suggestive of a more complex etiology.¹³ A required postmarket safety study in patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib will include assessment and management of nausea, diarrhea, vomiting, thiamine deficiency, and encephalopathy. Labeling that includes a boxed warning will be used to communicate the serious risk of serious and fatal encephalopathy, including Wernicke's. Labeling also includes the need to assess thiamine levels in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated, not to start fedratinib in patients with thiamine deficiency and to replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue fedratinib and initiate parenteral thiamine. Patients should be monitored until symptoms resolve or improve and thiamine levels normalize.

Furthermore, although Wernicke's encephalopathy is an uncommon adverse event related to a drug, this serious risk was recently added as a boxed warning in the Trisenox (arsenic trioxide) label and a REMS was not required to mitigate this risk.¹⁷ In addition, the likely prescribers will be hematologists and oncologists who should have experience in prescribing kinase inhibitors and managing drug induced neurotoxicity including encephalopathy. Based on the efficacy of fedratinib for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis, DRISK and DHP recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

DRISK and DHP have determined that a REMS is not necessary to ensure the benefits of fedratinib outweigh the risks. The required postmarket safety study will include assessment and management of nausea, diarrhea, vomiting, thiamine deficiency, and encephalopathy and may provide a better understanding of strategies that can be used to mitigate the risk of encephalopathy including Wernicke's. The likely prescribers will be hematologists and oncologists who should have experience in prescribing kinase inhibitors and managing drug related neurotoxicity including encephalopathy. At the time of this review, evaluation of safety information and labeling was ongoing. Should DHP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

- ¹ Proposed prescribing information for fedratinib as currently edited by FDA, Accessed 7/23/2019.
- ² National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Myeloproliferative neoplasms (version 2.2019 – October 29, 2018). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf (accessed 2019 June 16).
- ³ O'Sullivan JM, Harrison CN. Myelofibrosis: clinicopathologic features, prognosis, and management. *Clin Adv Hematol Oncol*. 2018;16(2):121-131.
- ⁴ Tefferi A. Primary myelofibrosis: 2019 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2018;93(12):1551-1560.
- ⁵ Mehta J, Wang H, Iqbal SU, Mesa R. Epidemiology of myeloproliferative neoplasms in the United States. *Leuk Lymphoma*. 2014;55(3):595-600.
- ⁶ Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood*. 2014;124(16):2507-13.
- ⁷ Jakafi (ruxolitinib) package insert. Wilmington, DE: Incyte Corporation; 2019 May.
- ⁸ Ayache S, Fernandes L. Division of Hematology Products (DHP). Inrebic (fedratinib). Mid-Cycle Meeting, clinical and statistics reviewer slides. April 10, 2019.
- ⁹ Impact Biomedicines, Inc., a wholly-owned subsidiary of Celgene Corporation. Fedratinib. Module 2.5. clinical overview. January 3, 2019.
- ¹⁰ Ayache, S. Division of Hematology Products (DHP). Fedratinib. Electronic communication. June 14, 2019.
- ¹¹ Division of Neurology Products consult to NDA 212327. May 1, 2019.

¹² Impact Biomedicines, Inc., a wholly-owned subsidiary of Celgene Corporation. Fedratinib. Module 2.7.4 summary of clinical safety. January 3, 2019.

¹³ Fedratinib multi-disciplinary review and evaluation. Accessed 8/6/2019.

¹⁴ Day GS, del Campo CM. Wernicke encephalopathy: a medical emergency. *CMAJ*. 2014;186(8):E295.

¹⁵ Thomson AD, Marshall EJ, Bell D. Time to act on the inadequate management of Wernicke's encephalopathy in the UK. *Alcohol*. 2013;48(1):4-8.

¹⁶ Donnino MW, Vega J, Miller J, Walsh M. Myths and misconceptions of Wernicke's encephalopathy: what every emergency physician should know. *Ann Emerg Med*. 2007;50(6):715-21.

¹⁷ Trisenox (arsenic trioxide) package insert. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2019 June.

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/s/

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I concur.

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Internal Consults

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Kate Heinrich Oswell, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Robert Nguyen, PharmD, Regulatory Review Officer, OPDP

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CDER-OPDP-RPM

Date: June 13, 2019

Re: NDA 212327
INREBIC® (fedratinib) capsules, for oral use

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