

CADTH REIMBURSEMENT REVIEW

Clinician Input

INREBIC (fedratinib)

(Celgene Inc., a Bristol Myers Squibb Company)

Indication: For the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, including patients who have been previously exposed to ruxolitinib.

November 26, 2020

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the view of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting clinician group and all conflicts of interest information from individuals who contributed to the content are included in the posted clinician group submission.

Clinician Input Template for CADTH pan-Canadian Oncology Drug Review Program

Before completing this template, be sure to [register](http://www.cadth.ca/pcodr/registration) with the pCODR program. Please visit www.cadth.ca/pcodr/registration for information about the registration process.

1. About the Registered Clinician

| | |
|---|--------------------------------------|
| Name of Registered Clinician | Dr. Tom Kouroukis |
| Title | Hematologist |
| Disease Specialty (if applicable) | Hematology |
| Province | Ontario |
| Organization Membership (if applicable, national or provincial) | Ontario Health (Cancer Care Ontario) |
| Email | [REDACTED] |
| Telephone Number | |

If this is a joint clinician input submission, please indicate the organization this submission is on behalf of, as well as list the names of the other clinicians and disease site specialty (if applicable). Please note that all clinicians listed must also register with CADTH and complete conflict of interest declaration forms.

with Dr. Anca Prica, Dr. Janet MacEachern, Dr. Lee Mozessohn, Dr. Mark Brown (Pharmacist) on behalf of Ontario Health-Cancer Care Ontario Hematology Cancer Drug Advisory Committee (DAC).

Confirmation of Authorship

I declare that I am the author of this submission and I confirm that no other parties have written or participated in the writing of the submission, except for those abovenamed in this joint submission (if applicable).

[REDACTED]

Signature

2020/11/26

Date (YYYY/MM/DD)

2. About the Drug and Indication Under Review

| | |
|---|--|
| CADTH pCODR Project Number | pCODR 10205 |
| Generic Drug Name (Brand Name) | Fedratinib (Inrebic) |
| Indication | For the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, including patients who have been previously exposed to ruxolitinib. |
| Funding Request | Same as indication |
| Trial(s) Being Submitted to pCODR ^a | <ul style="list-style-type: none"> JAKARTA (NCT01437787); Pardanani et al JAMA Oncol 2015. JAKARTA-2 (NCT01523171); Harrison et al, Lancet Haematol Jul 2017; Harrison et al J Clin Oncol 2019 [abstract]. |
| Health Canada Status | Approved (2020-07-27) |
| FDA | Approved (2019-08-16) |
| European Medicines Agency Status | Approved (2019-12-20) |
| Practice Guidelines ^a | NCCN Guidelines Myeloproliferative Neoplasms , ESMO Clinical Practice Guidelines: Haematological Malignancies |
| Provincial Funding of Current Treatments or Funding Algorithm | Ruxolitinib is funded in almost all jurisdictions for intermediate to high risk symptomatic myelofibrosis as assessed using the Dynamic International Prognostic Scoring System (DIPSS) Plus or patients with symptomatic splenomegaly. Some patients may receive hydroxyurea or best supportive care. |

^a Please note that access to some online publications require subscription.

3. Key Questions for Clinician Input

3.1 Current Treatment(s) for the Indication Under Review:

- If this is different than what is listed in the Provincial Funding of Current Treatments or Funding Algorithm on the previous page, identify the treatment(s) you would use.
- If more than one treatment is funded in your province, identify the treatment(s) that would be the most appropriate comparator for the drug under review.

Selected patients may proceed to allo transplant.
Pegylated interferon alfa 2a is not publicly funded currently but available as a treatment option via private pay.

3.2 Eligible Patient Population

Describe the patients for whom you would use the new treatment. Examples can include, but are not limited to, the following questions:

- Does the patient population in the reimbursement request align with the need identified in your clinical practice? Is there an unmet need?
- Can the inclusion and exclusion criteria of the clinical trial be applied in clinical practice?
- Is there a subgroup of patients beyond the study population that you would like to use the new treatment in? Is there a subgroup of patients within the study population that the new treatment should be limited to?
- **Implementation Questions: In clinical practice, is there evidence to extend the use of fedratinib to (provided all other eligibility criteria are met):**
 - a) Patients with an ECOG PS of 3 (to align with criteria from the ruxolitinib review);
 - b) Patients with low-risk or intermediate-risk level 2 symptomatic myelofibrosis;
 - c) Patients with prior treatment with a Janus Kinase 2 (JAK2) inhibitor.

The study population aligns with clinical practice. No specific subgroups to extend or limit treatment to.

Re: ECOG PS of 3 – reasonable to align with criteria from ruxolitinib review

Re: risk categories – align with study population – JAKARTA-2 included intermediate-1, intermediate-2 and high-risk patients

JAKARTA-2 has inclusion criteria that patients must be on ruxolitinib for at least 2 weeks.

There should be some flexibility around patient's blood count and treatment with fedratinib.

3.3 Relevance to Clinical Practice

Do you have experience with using the treatment (through clinical trials, manufacturer's access program, private drug insurance) under review?

☒ Yes ☐ No

- How or when would you use the new treatment? Is there any population/subpopulation where you particularly want to use this drug?
- How is the new treatment different than currently available treatments with respect to efficacy, safety, and tolerability?
- Are there contraindications to using the new treatment? Are there contraindications to current treatments that would make the new treatment favourable?

Please note: Scientific published references are not required, as pCODR has access to current scientific literature through the manufacturer's submission and a rigorous, independent literature search.

Fedratinib can be used any time. May want to use ruxolitinib first line and then use fedratinib second line.

No direct evidence how fedratinib compares with ruxolitinib in the first-line setting.

Fedratinib carries a serious warning re: serious and fatal encephalopathy, including Wernicke's.

3.4 Sequencing and Priority of Treatments

- Please describe how the new treatment could be sequenced with current treatment(s), if appropriate.
- In your opinion, in the event that the drug under review becomes available for funding in your jurisdiction, would the new treatment be a replacement of current treatment(s) or another option?
- **Implementation Questions: Please consider if there is evidence to support the optimal treatment sequencing with fedratinib with available treatments for myelofibrosis (i.e., hydroxyurea, ruxolitinib):**
 - a) Is there a preference to use fedratinib as an additional option (in the first-line setting as a replacement to ruxolitinib) or an additional line of therapy (following ruxolitinib treatment)?
 - b) In what clinical scenarios would ruxolitinib or fedratinib be the preferred first-line treatment for intermediate myelofibrosis? Please comment on the preference considering patient preference, efficacy, safety, and administration.
 - c) What are the available treatment options following progression on fedratinib (e.g., ruxolitinib)?

The preference may be to use ruxolitinib first-line and fedratinib after. Currently there's no data on using ruxolitinib post fedratinib. Hydroxyurea, pegylated interferon, or other supportive care measures and/or allo transplant in selective patients are treatment options post fedratinib.

3.5 Companion Diagnostic Testing

- If companion diagnostic testing is required for the new drug, is the test available in your jurisdiction? Is it funded by your jurisdiction? What concerns, if any, do you have on the test and turnaround time for test results? Are there specific considerations to a testing algorithm that you think would be important to share with the pCODR Expert Review Committee?

No companion diagnostic testing required

4. Implementation Questions

The Ministries of Health and provincial cancer programs across Canada are concerned about the sustainability of high-quality cancer control services. The rising cost of cancer drugs is becoming a major challenge to the sustainability of cancer care funding. While tremendous progress has been made in recent years in the cancer drug system, more is needed to be done to ensure innovative treatments are available to patients, while ensuring value for money for the public.

We are seeking your clinical opinion on the following implementation issues, if and when the new treatment is reimbursed. Your responses would be taken into consideration, among other factors, when Ministries of Health and provincial cancer programs make their final funding decisions.

- 4.1 In the JAKARTA trial, encephalopathy was reported with treatment with fedratinib at 500 mg daily. Is there evidence to support in clinical practice, whether there is a patient population that is at higher risk of developing encephalopathy, for whom fedratinib should not be used?**

Patients who have neurological impairment or nutritional issues may not be candidates for fedratinib.

- 4.2 The JAKARTA trial allowed treatment with fedratinib until disease progression or unacceptable toxicity. Patients were assessed at 6 months to determine response to therapy. In clinical practice, is there evidence to support:**

- What treatment discontinuation criteria would be used?**
- What assessment score tool is currently used to determine response to treatment (i.e., does this align with what was used in the JAKARTA trial)? What assessment score tool is recommended to determine response to treatment?**
- What is the recommended frequency of scans to determine response?**

- Treatment discontinuation can be based on disease progression or serious treatment toxicities.
- The MF symptom assessment forms are not routinely used in practice.
- Splenic volume calculation may not be routinely available; some objective measures which show a reduction in spleen size (clinical exam, ultrasound, CT, etc) will be reasonable to determine response.

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: **Dr. Tom Kouroukis**

Name of drug and indication under review: **Fedratrinib/Myelofibrosis**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

- Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

- ☐ Yes
☒ No

If no, please go to Section B.

- What form of payment did you receive? (Check all that apply.)

- ☐ Advisory role (e.g., advisory boards, health technology assessment submission advice) ☐ Program or Operating Funding (e.g., website)
☐ Conference attendance ☐ Research/educational grants
☐ Royalties ☐ Travel grants
☐ Gifts ☐ Sponsorship of events
☐ Honoraria ☐ Other, please specify: _____

- Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

| Company | Nature or description of activities or interests | Check Appropriate Dollar Range | | | |
|---------|--|--------------------------------|--------------------------|--------------------------|--------------------------|
| | | \$0 to 5,000 | \$5,001 to 10,000 | \$10,001 to 50,000 | In Excess of \$50,000 |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than \$10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

None

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

None

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge



Nov 5, 2020

Dr. Tom Kouroukis

Date

Name

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: **Dr. Anca Prica**

Name of drug and indication under review: **Fedratinib/Myelofibrosis**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

4. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

- ☐ Yes
☒ No

If no, please go to Section B.

5. What form of payment did you receive? (Check all that apply.)

- | | |
|--|---|
| <input type="checkbox"/> Advisory role (e.g., advisory boards, health technology assessment submission advice) | <input type="checkbox"/> Program or Operating Funding (e.g., website) |
| <input type="checkbox"/> Conference attendance | <input type="checkbox"/> Research/educational grants |
| <input type="checkbox"/> Royalties | <input type="checkbox"/> Travel grants |
| <input type="checkbox"/> Gifts | <input type="checkbox"/> Sponsorship of events |
| <input type="checkbox"/> Honoraria | <input type="checkbox"/> Other, please specify: _____ |

6. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

| Company | Nature or description of activities or interests | Check Appropriate Dollar Range | | | |
|---------|--|--------------------------------|--------------------------|--------------------------|--------------------------|
| | | \$0 to 5,000 | \$5,001 to 10,000 | \$10,001 to 50,000 | In Excess of \$50,000 |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than \$10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

None

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

None

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge



Nov 5, 2020

Dr. Anca Prica

Date

Name

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: **Dr. Janet MacEachern**

Name of drug and indication under review: **Fedratinib/Myelofibrosis**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

7. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

- ☐ Yes
☒ No

If no, please go to Section B.

8. What form of payment did you receive? (Check all that apply.)

- | | |
|--|---|
| <input type="checkbox"/> Advisory role (e.g., advisory boards, health technology assessment submission advice) | <input type="checkbox"/> Program or Operating Funding (e.g., website) |
| <input type="checkbox"/> Conference attendance | <input type="checkbox"/> Research/educational grants |
| <input type="checkbox"/> Royalties | <input type="checkbox"/> Travel grants |
| <input type="checkbox"/> Gifts | <input type="checkbox"/> Sponsorship of events |
| <input type="checkbox"/> Honoraria | <input type="checkbox"/> Other, please specify: _____ |

9. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

| Company | Nature or description of activities or interests | Check Appropriate Dollar Range | | | |
|---------|--|--------------------------------|--------------------------|--------------------------|--------------------------|
| | | \$0 to 5,000 | \$5,001 to 10,000 | \$10,001 to 50,000 | In Excess of \$50,000 |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than \$10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

None

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

None

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge



Nov 5, 2020

Dr. Janet MacEachern

Date

Name

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: Dr. Lee Mozessohn

Name of drug and indication under review: Fedratinib/Myelofibrosis

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

10. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

- ☐ Yes
☒ No

If no, please go to Section B.

11. What form of payment did you receive? (Check all that apply.)

- ☐ Advisory role (e.g., advisory boards, health technology assessment submission advice) ☐ Program or Operating Funding (e.g., website)
☐ Conference attendance ☐ Research/educational grants
☐ Royalties ☐ Travel grants
☐ Gifts ☐ Sponsorship of events
☐ Honoraria ☐ Other, please specify: _____

12. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

| Company | Nature or description of activities or interests | Check Appropriate Dollar Range | | | |
|---------|--|--------------------------------|--------------------------|--------------------------|--------------------------|
| | | \$0 to 5,000 | \$5,001 to 10,000 | \$10,001 to 50,000 | In Excess of \$50,000 |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than \$10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

None

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

None

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge



November 5, 2020

Dr. Lee Mozessohn

Date

Name

Appendix A: pCODR Clinician Conflict of Interest Declarations

Please note: Each registered clinician must complete their own separate pCODR Clinician Conflict of Interest Declarations Template even if the submission is made jointly.

Name of registered clinician: **Dr. Mark Brown (Pharmacist)**

Name of drug and indication under review: **Fedratinib/Myelofibrosis**

Conflict of Interest Declaration

To maintain the objectivity and credibility of the pCODR process, all participants in the pCODR review process must disclose any conflicts of interest. A registered clinician must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. A conflict of interest declaration is requested for transparency — it does not negate or preclude the use of the clinician input.

Examples of conflicts of interest include, but are not limited to:

- financial support from the pharmaceutical industry or other entities (e.g., educational or research grants, honoraria, gifts, and salary)
- affiliations, or personal or commercial relationships with drug manufacturers or other interest groups.

Section A: Payment Received

13. Have you received any payments over the previous two years from any company or organization that may have a direct or indirect interest in the drug under review?

- ☐ Yes
☒ No

If no, please go to Section B.

14. What form of payment did you receive? (Check all that apply.)

- ☐ Advisory role (e.g., advisory boards, health technology assessment submission advice) ☐ Program or Operating Funding (e.g., website)
☐ Conference attendance ☐ Research/educational grants
☐ Royalties ☐ Travel grants
☐ Gifts ☐ Sponsorship of events
☐ Honoraria ☐ Other, please specify: _____

15. Please provide the names of companies and organizations, and the amounts of the payments, in the following table.

| Company | Nature or description of activities or interests | Check Appropriate Dollar Range | | | |
|---------|--|--------------------------------|--------------------------|--------------------------|--------------------------|
| | | \$0 to 5,000 | \$5,001 to 10,000 | \$10,001 to 50,000 | In Excess of \$50,000 |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Section B: Holdings or Other Interests

Have you received or are in possession of stocks or options of more than \$10,000 (excluding mutual funds) for organizations that may have a direct or indirect interest in the drug under review? If yes, please list them in the following box.

None

Section C: Affiliations, Personal or Commercial Relationships

Do you have personal or commercial relationships either with a drug or health technology manufacturer (including the manufacturer's parent corporation, subsidiaries, affiliates, and associated corporations) or other interest groups? If yes, please provide the names of the companies and organizations, and outline the nature of these relationships, in the following box.

None

By checking this box, I hereby certify that the information that I have presented here is accurate and complete to the best of my knowledge



Nov 5, 2020

Dr. Mark Brown

Date

Name