Regimen Monograph

A - Regimen Name

FEDR Regimen

Fedratinib

Disease Site

Hematologic
Myeloproliferative Neoplasms (MPNs)

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of splenomegaly and/or disease related symptoms of intermediate-2 or high-risk primary myelofibrosis (MF), post-polycythemia vera MF, or post-essential thrombocythemia MF, in patients with good performance status who have contraindications to ruxolitinib or have developed intolerances to ruxolitinib (without disease progression)

Supplementary Public Funding

fedratinib
Exceptional Access Program (fedratinib - For the treatment of splenomegaly and/or disease related symptoms of myelofibrosis according to clinical criteria) (EAP Website)

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B - Drug Regimen

fedratinib	400 mg	PO	Daily

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Start fedratinib when platelets are $\geq$ 50 x 10^9/L at baseline.

Do not start treatment in patients with thiamine deficiency.

Patients who are on treatment with ruxolitinib before the initiation of fedratinib must taper and discontinue according to the ruxolitinib product monograph. Also refer to the Canadian MPN group consensus document (Gupta et al, 2020).

Refer to Interactions section for dosing recommendations when co-administered with strong and moderate CYP3A4 inhibitors.

Dosage with toxicity

Dose Levels

Dose Level	Fedratinib Dose* (mg daily)
0	400
-1	300
-2	200
-3	Discontinue

*May re-escalate if toxicity resolved for ≥ 28 days, up to the original dose level. Do not re-escalate more than once per month. Do not re-escalate if reduction was due to Grade 4 non-hematologic toxicity, Grade 3 or 4 ALT, AST, or bilirubin ↑, or recurrent Grade 4 hematologic toxicity.

Consider dose reduction for patients who become transfusion dependent during fedratinib treatment.

Toxicity	Severity/Grade	Action†
Thrombocytopenia	Platelets 25 - 49 x 10^9/L with active bleeding	Hold* dose. Restart at 1 dose level ↓.
	Platelets < 25 x 10^9/L	
Neutropenia	ANC < 0.5 x 10^9/L	Hold* dose. Restart at 1 dose level ↓. Consider G-CSFs.
Anemia	Hgb < 80 g/L OR transfusion indicated	Hold* dose. Restart at 1 dose level ↓.
Nausea, Vomiting, or Diarrhea	Grade ≥ 3 not responding to supportive measures within 48 hours	Hold* dose. Restart at 1 dose level ↓.
↑ ALT, AST, or Bilirubin	Grade 3 or 4	Hold* dose. Restart at 1 dose level ↓. Monitor q2 weeks for at least 3 months after dose reduction. If recurs, discontinue.
Thiamine (vitamin B1) deficiency	Thiamine levels < normal but ≥ 30 nmol/L, without signs and symptoms of Wernicke's encephalopathy (WE)	Hold* dose. Initiate thiamine PO 100 mg daily until levels are within normal range, then consider restarting fedratinib.

	Thiamine levels < 30 nmol/L, without signs and symptoms of WE	Hold* dose. Initiate parenteral thiamine until levels are within normal range, then consider restarting fedratinib.
	Any signs and symptoms of WE regardless of thiamine levels	Discontinue. Initiate parenteral thiamine.
Other Non-Hematologic Toxicities	Grade 3 or 4	Hold* dose. Restart at 1 dose level ↓.

*Do not restart until hematologic toxicity ≤ Grade 2 or baseline, non-hematologic toxicity ≤ Grade 1 or baseline, and thiamine levels are within normal range.

†May re-escalate if toxicity resolved for ≥ 28 days, up to the original dose level. Do not re-escalate more than once per month. Do not re-escalate if reduction was due to Grade 4 non-hematologic toxicity, Grade 3 or 4 ALT, AST, or bilirubin ↑, or recurrent Grade 4 hematologic toxicity.

Hepatic Impairment

Pharmacokinetics of fedratinib has not been evaluated in patients with severe hepatic impairment.

Bilirubin		AST	Fedratinib Starting Dose
≤ ULN	and	> ULN	No adjustment required
1 to 1.5 x ULN	and	Any	
>1.5 to 3 x ULN	and	Any	No adjustment required; monitor for increased toxicity
>3 x ULN	and	Any	No data; avoid use

Renal Impairment

Creatinine Clearance (mL/min)	Fedratinib Starting Dose
≥ 60	No adjustment required
30 - 59	No adjustment required; monitor for increased toxicity
15 - 29	200 mg once daily
< 15	No data

Dosage in the Elderly

No dose adjustment required. No overall differences in safety or effectiveness were observed between older and younger patients.

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F - Adverse Effects

Refer to fedratinib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea • Nausea, vomiting	• Anemia (may be severe)	• Fatigue • Myelosuppression ± infection, bleeding (may be severe) • Constipation • Creatinine increased • Headache • Musculoskeletal pain • Pruritus • ↑ Amylase / lipase (may be severe)	• Atrial fibrillation • Cardiotoxicity • Pleural effusion • Renal failure • Pancreatitis • Encephalopathy (Wernicke's)

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G - Interactions

Refer to fedratinib drug monograph(s) for additional details.

- Reduce fedratinib dose to 200 mg when co-administered with strong CYP3A4 inhibitors, and to 300 mg when co-administered with moderate CYP3A4 inhibitors. If the strong or moderate inhibitor is discontinued, may re-escalate fedratinib in 100 mg increments (Refer to Dose Levels table).
- Avoid co-administration with strong CYP2C19 inhibitors and combined CYP2C19/3A4 inhibitors due to ↑ risk of fedratinib toxicity.
- Avoid co-administration with strong or moderate CYP3A4 inducers due to ↓ fedratinib effect.
- Caution when used with CYP3A4, CYP2D6 and CYP2C19 substrates, due to possible ↑ in substrate exposure. Monitor for substrate toxicity.
- Monitor for increased effect and toxicity of substrates when co-administered with OCT2 and MATE1/2-K substrates (e.g., blood glucose levels with metformin).

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H - Drug Administration and Special Precautions

Refer to fedratinib drug monograph(s) for additional details.

Administration

- Fedratinib may be taken with or without food. Taking with food (high fat evening meal) may help reduce nausea and vomiting.
- Capsules should be swallowed whole and not broken, opened or chewed.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during fedratinib treatment.
- If a dose is missed, this dose should be skipped. The next dose should be taken at the scheduled time the following day. Two doses should not be taken at the same time to make up for a missed dose.
- Store at room temperature (15 to 30°C).

Contraindications

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions

- Major adverse cardiovascular events (MACE), arterial/venous thrombosis, and/or malignancy, including fatal outcomes, have been reported with the JAK inhibitor tofacitinib. Consider the benefits and risks prior to initiating, or continuing, therapy of JAK inhibitors, especially in patients > 65 years, who are current or past smokers, or with other cardiovascular, thrombosis or malignancy risk factors.
- Encephalopathy, including Wernicke's, has been reported with fedratinib. Any mental status changes should be assessed, including neurologic exam, thiamine levels and imaging, for potential encephalopathy.
- Fedratinib has not been studied in patients with a baseline platelet count < 50 x 10^9/L.

Pregnancy/Lactation

- Fedratinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **1 month** after the last dose.
- Breastfeeding is not recommended during treatment and for at least **1 month** after the last dose.
- Fertility effects: Unknown

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline and at each visit
- Liver function tests; Baseline and as clinically indicated. After a dose reduction: every 2 weeks for at least 3 months
- Thiamine level; Baseline, monthly for the first 3 months, then every 3 months, and as clinically indicated
- Renal function tests; Baseline and as clinically indicated
- Amylase and lipase; Baseline and as clinically indicated

- Clinical toxicity assessment for anemia, infections, bleeding, arterlial and venous thrombosis, secondary malignancies, cardiac, GI, and neurologic effects; At each visit

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K - References

Fedratinib drug monograph. Ontario Health (Cancer Care Ontario).

Gupta V, Cerquozzi S, Foltz L, et al. Patterns of ruxolitinib therapy failure and its management in myelofibrosis: perspectives of the Canadian Myeloproliferative Neoplasm Group. JCO Oncol Pract 2020 Jul;16(7):351-359.

Pardanani A, Harrison C, Cortes JE, et al. Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis. JAMA Oncol. 2015;1(5):643-651. doi:10.1001/jamaoncol.2015.1590

April 2023 Expanded regimen monograph

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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