Drug Monograph

A - Drug Name

fedratinib

COMMON TRADE NAME(S): Inrebic®

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B - Mechanism of Action and Pharmacokinetics

Fedratinib is a selective inhibitor of Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). It has higher potency for JAK2 over JAK1, JAK3, and TYK2.

Myeloproliferative neoplasms (MPNs), including myelofibrosis and polycythemia vera, are associated with abnormal JAK2 activation. In JAK2 mutated cell models, fedratinib reduces phosphorylation of Signal Transducer and Activator of Transcription (STAT) 3 and 5 proteins, prevents cell proliferation, and induces apoptosis.

Absorption	Bioavailability	77%
	T max	2 hours (median; after single 400 mg dose)
	Time to reach steady state	within 15 days
	Effects with food	Food had no effect on drug exposure
Distribution	PPB	≥ 92%
Metabolism	Fedratinib is metabolized by multiple CYP enzymes and flavin-containing monooxygenases (FMOs).	
	Active metabolites	Yes

	Inactive metabolites	Yes
Elimination	Half-life	~62-78 hours (terminal)
	Feces	77% (23% unchanged)
	Urine	5% (3% unchanged)

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C - Indications and Status

Health Canada Approvals:

- Myelofibrosis (MF)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

The following adverse effect were reported with an incidence ≥ 5% in a pooled cohort of patients with MF during Phase 2 and Phase 3 studies. This table also includes severe or life-threatening adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (2%)	E
	Cardiac arrest (rare)	E
	Cardiogenic shock (rare)	E
	Heart failure (3%)	E
Dermatological	Pruritus (10%)	E
Gastrointestinal	Constipation (16%)	E
	Diarrhea (63%) (5% severe)	E

	Nausea, vomiting (59%) (2% severe)	E
General	Fatigue (19%)	E
Hematological	Anemia (43%) (severe)	E D
	Myelosuppression ± infection, bleeding (17%) (severe)	E D
Hepatobiliary	↑ Amylase / lipase (10%) (severe)	E
	↑ LFTs (9%)	E
	Pancreatitis (1%)	E
Musculoskeletal	Muscle spasm (9%)	E
	Musculoskeletal pain (10%)	E
Nervous System	Dizziness (9%)	E
	Encephalopathy (including Wernicke's) (1% severe)	E
	Headache (10%)	E
Renal	Creatinine increased (10%)	E
	Renal failure (2%)	E
Respiratory	Pleural effusion (2%)	E
Urinary	Dysuria (6%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for fedratinib include diarrhea, nausea, vomiting, anemia, fatigue, myelosuppression ± infection, bleeding, and constipation.

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.

Serious and fatal **encephalopathy**, including Wernicke's, has been reported with fedratinib. Wernicke's encephalopathy is a neurological emergency caused by thiamine (Vitamin B1) deficiency. Signs and symptoms include ataxia, mental status changes (e.g., drowsiness, confusion, or memory impairment), and ophthalmoplegia (e.g., nystagmus and diplopia). Any mental status changes should be assessed, including neurologic exam, thiamine levels and imaging, for potential encephalopathy.

Anemia (new or worsening Grade 3) and **thrombocytopenia** (≥ Grade 3) with or without bleeding were reported with median times to onset of ~2 months.

Nausea, **vomiting**, and **diarrhea** were reported in clinical trials with a median time to onset of 5, 2 and 6 days, respectively. Consider antiemetic prophylaxis for the first 8 weeks of treatment and as clinically indicated.

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E - Dosing

Refer to protocol by which the patient is being treated.

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

Start fedratinib when platelets are ≥ 50 x 10^9/L at baseline.

Do not start treatment in patients with thiamine deficiency. All patients should receive prophylaxis with oral thiamine 100 mg daily while on fedratinib.

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).

Adults:

Oral: 400 mg Daily

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.

Dosage with 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

Dosage with 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.

Dosage based on gender:

No dose adjustment required. No clinical differences were observed based on sex. Incidences of GI adverse effects were higher in female than in male patients.

Dosage based on ethnicity:

No dose adjustment required. No clinical differences were observed based on race.

Children:

The safety and efficacy of fedratinib have not been established in children < 18 years of age.

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F - Administration Guidelines

- 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).

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G - Special Precautions

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.

Other Drug Properties:

- Carcinogenicity: Unknown
  Secondary malignancies were observed in patients with rheumatoid arthritis who used the JAK-inhibitor tofacitinib.
- Phototoxicity: No

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Pregnancy:
  Fedratinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 month** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **1 month** after the last dose.
- Fertility effects: Unknown

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H - Interactions

Fedratinib is metabolized by multiple CYPs *in vitro* (mainly by CYP3A4, with less contribution from CYP2D6 and CYP2C19) and flavin-containing monooxygenases (FMOs).

Fedratinib inhibits CYP3A4, CYP2D6, and CYP2C19.

In vitro, fedratinib is a substrate of P-gp and inhibits P-gp, BCRP, MATE1, MATE2-K, OATP1B1, OATP1B3, and OCT2.

No dose adjustment is necessary when fedratinib is given with drugs that increase gastric pH (such as antacids, H2 blockers, and proton pump inhibitors).

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, itraconazole, voriconazole and posaconazole)	↑ fedratinib concentration (↑ AUC by 2.5- to 3-fold)	↓ metabolism of fedratinib	Avoid. If must co-administer, ↓ fedratinib dose to 200 mg daily. If inhibitor is discontinued, ↑ fedratinib dose to 300 mg daily for 2 weeks, then to 400 mg daily as tolerated. Make additional dose adjustments as needed.
Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin)	↑ fedratinib concentration (↑ AUC by 1.1-fold)	↓ metabolism of fedratinib	Monitor for toxicity; adjust fedratinib dose as needed.
Combined CYP2C19 and CYP3A4 moderate inhibitors (e.g., fluconazole)	↑ fedratinib concentration	↓ metabolism of fedratinib	Avoid. If must co-administer, monitor for toxicity; adjust fedratinib dose as needed.
Strong or moderate CYP3A4 inducers (i.e. phenytoin, rifampin, efavirenz, St. John's Wort, etc)	↓ fedratinib exposure (↓ by 50% to 80%)	↑ metabolism of fedratinib	Avoid
CYP3A4, CYP2D6, and	↑ substrate exposure	↓ metabolism of substrate	Caution. Monitor for substrate toxicity.

CYP2C19 substrates (e.g., midazolam, omeprazole, metoprolol)			
OCT2 and MATE1/2-K substrates, (i.e., metformin)	↓ renal clearance of substrate (↓ by 36% with metformin)	Inhibition of drug transporter by fedratinib (in vitro)	Monitor for increased effect or toxicity of substrates (e.g., blood glucose levels with metformin)

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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

Monitor Type	Monitor Frequency
CBC	Baseline, at each visit, and as clinically indicated
Liver function tests	Baseline, at each visit, and as clinically indicated. After a dose reduction: every 2 weeks for at least 3 months.
Renal function tests	Baseline, at each visit, and as clinically indicated
Thiamine level	Baseline and as clinically indicated
Amylase and lipase	Baseline and as clinically indicated
Clinical toxicity assessment for anemia, infections, bleeding, arterial and venous thrombosis, secondary malignancies, cardiac, GI, and neurologic effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- fedratinib - For the treatment of splenomegaly and/or disease related symptoms of myelofibrosis according to clinical criteria

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K - References

European Medicines Agency. Assessment report: Inrebic (fedratinib). December 10, 2020.

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.

Health Professional Risk Communication. Janus Kinase Inhibitors and the Risk of Major Adverse Cardiovascular Events, Thrombosis (Including Fatal Events) and Malignancy. Health Canada. November 2022

Hesketh Paul J. et al. Antiemetics: ASCO Guideline Update. Journal of Clinical Oncology 2020 38:24, 2782-2797.

Pardanani A et al. Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2015 Aug;1(5):643-51.

Pardanani A et al. Updated results of the placebo-controlled, phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis. Br J Haematol. 2021 Oct;195(2):244-248.

Prescribing Information: Fedratinib (Inrebic®). Impact Biomedicines, Inc. December 2021.

Product Monograph: Fedratinib (Inrebic®). Celgene Inc. July 4, 2024.

Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A Comprehensive Overview of Globally Approved JAK Inhibitors. Pharmaceutics. 2022 May 6;14(5):1001.

Summary of Product Characteristics: Inrebic 100 mg hard capsules. Bristol Myers Squibb Pharmaceuticals Limited. November 2021.

January 2025 Updated Dosing, Pregnancy and Lactation, Interactions, and Monitoring sections

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L - Disclaimer

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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