DRUG NAME: Fedratinib

SYNONYM(S): SAR302503[1], TG101348[1]

COMMON TRADE NAME(S): INREBIC®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Fedratinib is an orally administered, selective inhibitor of Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). JAKs are a family of intracellular tyrosine kinases that mediate the signaling of cytokines and growth factors which are important for hematopoiesis and immune function. Myeloproliferative neoplasms are known to be associated with dysregulated JAK2 signaling. Fedratinib reduces phosphorylation of signal transducer and activator of transcription proteins, inhibits cell proliferation, and induces apoptosis in mutated JAK2 and FLT3 cell lines. Fedratinib has higher potency for JAK2 over family members JAK1, JAK3, and TYK2, and has activity against a broader family of kinases and kinase mutants.[1-5]

PHARMACOKINETICS:

Oral Absorption	~77%; T_{max} = 3 h	
Distribution	highly protein bound	
	cross blood brain barrier?	no information found
	volume of distribution	1770 L
	plasma protein binding	≥92%
Metabolism	predominantly metabolized by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily fecal elimination	
	urine	5% (3% unchanged)
	feces	77% (23% unchanged)
	terminal half life	114 h
	clearance	13 L/h
Elderly	no clinically significant difference	

Adapted from standard reference[1,4,5] unless specified otherwise.

USES:

Primary uses:

*Myeloproliferative neoplasms

Other uses:

*Health Canada approved indication

Developed: 1 June 2022
Revised: 1 September 2022

SPECIAL PRECAUTIONS:

Caution:

- ***Wernicke's encephalopathy,*** resulting from ***thiamine deficiency***, has been reported with fedratinib treatment; correct thiamine deficiency prior to starting treatment[4,5] (consider empiric thiamine supplementation if thiamine levels are unavailable)[6]
- patients with pre-existing ***renal*** or ***hepatic impairment*** require increased monitoring for fedratinib toxicity and may need starting dose adjustment[4,5]
- consider fedratinib dose reduction for ***drug interactions*** involving the CYP 3A4 metabolic pathway[4,5]
- thrombosis, secondary malignancies, and major adverse cardiac events are known ***class effects of JAK inhibitors;*** patients with risk factors or prior history of these conditions may be at increased risk of experiencing these events during treatment with fedratinib[5]

Carcinogenicity: Fedratinib is not carcinogenic in animal models.[4,5]

Mutagenicity: Not mutagenic in Ames test. Fedratinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4,5]

Fertility: In animal studies, there were no observed effects on estrous cycle parameters, mating performance, fertility, pregnancy rate, or reproductive parameters in males or females at exposures ~0.10 times the expected human exposure following recommended doses.[4,5] It is not known if fedratinib has any effect on reproductive parameters at exposures at or higher than the expected human exposure following recommended doses.

Pregnancy: In animal studies, post-implantation loss, lower fetal body weights, and skeletal variations were observed at exposures ~0.10 times the expected human exposure following recommended doses. Women of childbearing potential should use effective contraception during treatment and for at least one month after the last dose.[4,5]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for at least one month after the last dose.[4,5]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[3]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (40-99%, severe 30-43%); median time to onset of grade 3 events is 2 months (75% occur within 3 months)
	neutropenia (22-23%, severe 5-6%)
	thrombocytopenia (47-63%, severe 12-17%); median time to onset of grade 3 events is 1 month (75% occur within 4 months)
cardiac	atrial fibrillation (2%)
	cardiac failure (3-5%)
	cardiogenic shock (severe 1%); fatal events reported
gastrointestinal	*emetogenic potential:* moderate[8]

Developed: 1 June 2022
Revised: 1 September 2022

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
see paragraph following **Side Effects** table	abdominal pain (6-21%)
	constipation (16%, severe 1%)
	diarrhea (61-71%, severe 5%)
	nausea (46-81%, severe <1%)
	pancreatitis (<1%)
	rectal hemorrhage (<1%)
	vomiting (24-57%, severe 2-3%)
general disorders and administration site conditions	fatigue (19%, severe 5%)
infections and infestations	pneumonia (4%)
	sepsis (2%); fatal events reported
	urinary tract infection (6-9%)
investigations	amylase increase (20-24%, severe 2%); median time to onset is 15 days
	ALT increase (9-43%, severe 1-2%); median time to onset is 1 month
	AST increase (5-52%, severe 1%); median time to onset is 1 month
	bilirubin increase (29%, severe 2%)
	creatinine increase (10-68%, severe 1-3%)
	lipase increase (32-35%, severe 9-10%); median time to onset is 15 days
	weight increase (9%)
metabolism and nutrition	hyponatremia (26%, severe 5%)
musculoskeletal and connective tissue	bone pain (8%)
	muscle spasms (9-12%)
	pain in extremity (10%)
nervous system	dizziness (8-9%)
	encephalopathy, including Wernicke's encephalopathy (1%, severe <1%); see paragraph following **Side Effects** table
	headache (9-10%, severe <1%)
	hemorrhagic stroke (<1%)
renal and urinary	acute kidney injury (2%)
	dysuria (6%)
respiratory, thoracic and mediastinal	pleural effusion (2%)
skin and subcutaneous tissue	pruritus (10%)
vascular	hypertension (4%, severe 3%)

Adapted from standard reference[1,3-5] unless specified otherwise.

Developed: 1 June 2022
Revised: 1 September 2022

Serious and fatal ***encephalopathy,*** including ***Wernicke's encephalopathy***, is reported with fedratinib. Wernicke's encephalopathy is a neurologic emergency resulting from thiamine (vitamin B1) deficiency, with signs and symptoms including ataxia, mental status changes, and ophthalmoplegia (e.g., nystagmus, diplopia). Diarrhea and vomiting associated with fedratinib treatment may contribute to lower thiamine levels. Thiamine deficiency should be corrected prior to starting fedratinib and regular monitoring of thiamine levels is recommended during treatment.[4,5] Consider empiric thiamine supplementation if thiamine testing is unavailable.[6] Patients reporting rapid weight loss or any change in mental status including drowsiness, confusion, or memory impairment should be promptly evaluated for potential encephalopathy. Discontinue fedratinib if Wernicke's encephalopathy is suspected.[4,5]

Gastrointestinal adverse events are reported in up to 81% of patients, and may occur more frequently in female patients. Nausea, vomiting, and diarrhea are most commonly reported and have a median time to onset of 2-6 days after starting treatment. Most reactions are grade 1 or 2. Nausea and vomiting may be minimized by administering fedratinib with a high-fat evening meal. Prophylactic antiemetics are recommended for at least the first 8 weeks of treatment and then as clinically indicated. Antidiarrheal medications are recommended at the first onset of symptoms. Fedratinib dose interruption and/or reduction may be required to manage symptoms.[4,5]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
efavirenz[4,5]	47-50% decrease in AUC of fedratinib	moderate induction of CYP 3A4 by efavirenz	avoid concurrent use
grapefruit juice[4]	may increase plasma level of fedratinib	may inhibit CYP 3A4 metabolism of fedratinib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of fedratinib therapy
ketoconazole[4,5]	3-fold increase in AUC of fedratinib	strong inhibition of CYP 3A4 by ketoconazole	reduce fedratinib dose to 200 mg PO once daily and monitor for fedratinib toxicity
metformin[4,5]	36% decrease in renal clearance of metformin; 51% increase in AUC and 27% increase in C_{max} of baseline adjusted plasma glucose	inhibition of OCT2, MATE1, and MATE2-K by fedratinib	dose modification of metformin may be required; monitor blood glucose levels regularly
metoprolol[4,5]	2-fold increase in AUC of metoprolol	inhibition of CYP 2D6 by fedratinib	dose modification of metoprolol may be required; monitor blood pressure and heart rate
midazolam[4,5]	4-fold increase in AUC of midazolam	inhibition of CYP 3A4 by fedratinib	dose modification of midazolam may be required; monitor for midazolam toxicity
omeprazole[4,5]	3-fold increase in AUC of omeprazole by fedratinib	inhibition of CYP 2C19 by fedratinib	dose modification of omeprazole may be required; monitor for omeprazole toxicity
pantoprazole[4,5]	1.15-fold increase in AUC of fedratinib	increase in gastric pH by pantoprazole	dose adjustment not required
rifampicin[4,5]	80-81% decrease in AUC of fedratinib	strong induction of CYP 3A4 by rifampicin	avoid concurrent use

Fedratinib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of fedratinib. If coadministration with a ***moderate*** CYP 3A4 inhibitor cannot be avoided, reduce fedratinib dose to 300 mg PO once daily[4]. If coadministration with a

Developed: 1 June 2022
Revised: 1 September 2022

strong CYP 3A4 inhibitor cannot be avoided, reduce fedratinib dose to 200 mg PO once daily[4,5]. After discontinuation of the concurrent inhibitor, fedratinib dose may be re-escalated in 100 mg increments as clinically indicated to a maximum of 400 mg.[4]

CYP 3A4 ***inducers*** may decrease the plasma concentration of fedratinib. Avoid concurrent use with moderate or strong CYP 3A4 inducers if possible.[4,5]

Fedratinib is an ***inhibitor*** of ***CYP 3A4***, ***CYP 2D6***, and ***CYP 2C19*** and may increase the plasma concentration of substrates of these enzymes. Dose modification of the concomitant substrate may be required. Monitor for toxicity from the substrate drug.[4]

Fedratinib may decrease renal clearance of drugs that are excreted via OCT2 and MATE1/2-K; clinical significance is unknown. Monitor for toxicity from the substrate drug.[4,5]

Fedratinib is a substrate of CYP 2C19. Inhibitors of CYP 2C19 may increase the plasma concentration of fedratinib; clinical significance is unknown.[4,5] Monitor for fedratinib toxicity.

Fedratinib is a substrate of P-glycoprotein (P-gp) in vitro; clinical significance is unknown.[4,5]

Fedratinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1, and OCT2 in vitro; clinical significance is unknown.[4,5]

SUPPLY AND STORAGE:

Oral: Celgene Inc. supplies fedratinib as 100 mg capsules. Store at room temperature.[4]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:[4-6]

400 mg (range 200-400 mg) ***PO once daily****

Administer with food or on an empty stomach. Administration with food, particularly with a high-fat evening meal, may reduce nausea and vomiting.

*dose adjustment may be required for some drug interactions

Concurrent radiation:

no information found

Dosage in myelosuppression:

modify according to protocol by which patient is being treated

Dosage in renal failure:[4,5]

Creatinine Clearance (mL/min)	Starting Dose
>60	100%
30-59	100%; monitor for increased toxicity
15-29	200 mg PO daily; monitor for increased toxicity

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Developed: 1 June 2022
Revised: 1 September 2022

BC Cancer usual dose noted in ***bold, italics***

Dosage in hepatic failure:[4,5]	mild impairment: no adjustment required moderate impairment: no adjustment required; monitor for increased toxicity severe impairment: no information found; monitor for increased toxicity
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established[4]

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Fedratinib. Wolters Kluwer Clinical Drug Information Inc., 2022. Available at: online.lexi.com. Accessed February 22, 2022
2. AHFS Drug Information® - Lexicomp Online (database on the Internet). Fedratinib. Wolters Kluwer Clinical Drug Information Inc., 2021. Available at: online.lexi.com. Accessed February 22, 2022
3. 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
4. Celgene Inc. INREBIC® product monograph. Montreal, Canada; September 9, 2021
5. Impact Biomedicines Inc. INREBIC® full prescribing information. Summit, NJ, USA; December 2021
6. BC Cancer Leukemia/BMT Tumour Group. (ULKMFFED) BC Cancer Protocol Summary for Treatment of Symptomatic Myelofibrosis with Fedratinib . Vancouver, British Columbia: BC Cancer; September 1, 2022
7. Lynda Foltz MD. Division of Hematology, St. Paul's Hospital. Personal communication. April 24,2022
8. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020

Developed: 1 June 2022
Revised: 1 September 2022