DRUG NAME: Ruxolitinib

SYNONYM(S): ruxolitinib phosphate,[1] INCB018424[2]

COMMON TRADE NAME(S): JAKAVI®,[3] JAKAFI® (USA)[1]

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Ruxolitinib is a kinase inhibitor which selectively inhibits Janus Associated Kinases (JAKs), JAK1 and JAK2.[3,4] JAKs mediate the signaling pathway of cytokines and growth factors for hematopoiesis and immune function. In myelofibrosis, the dysregulation of the JAK1 and JAK2 signaling leads to impaired hematopoiesis and immune function. Ruxolitinib modulates the cytokine-stimulated signaling through the inhibition of JAK1 and JAK2.[3]

PHARMACOKINETICS:

Oral Absorption[3,4]	95% or greater; time to peak: 1-2 h	
Distribution[1,3]	extensive	
	cross blood brain barrier?	no information found
	volume of distribution	53-65 L
	plasma protein binding	97%, mostly to albumin
Metabolism	primarily through CYP 3A4 pathway	
	active metabolite(s)	2 major metabolites, unnamed
	inactive metabolite(s)	none specified
Excretion[3,4]	primarily through metabolism; <1% unchanged drug	
	urine	74%
	feces	22%
	terminal half life	3-6 h including metabolites; prolonged in hepatic impairment
	clearance	women:18 L/h; men:22L/h

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

*Myeloproliferative disorders

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- use with caution in patients with a low heart rate at baseline(<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure; avoid concomitant medications that result in a decrease in heart rate and/or PR interval prolongation[3]
- avoid abrupt discontinuation; taper gradually to prevent rapid return of myelofibrosis symptoms[3,5,6]

- starting dose reduction recommended for patients with ***hepatic impairment*** or moderate to severe ***renal impairment***[3]
- review concurrent medication for potential drug interactions via CYP 3A4

Carcinogenicity: Ruxolitinib is not carcinogenic in mouse model.[3]

Mutagenicity: Not mutagenic in Ames test. Ruxolitinib is not clastogenic in mammalian *in vitro* or *in vivo* chromosome tests.[3]

Fertility: No information found.

Pregnancy: FDA Pregnancy Category C.[4] Animal studies have shown fetal risks and there are no controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. Ruxolitinib is associated with maternal toxicity, embryolethality, and fetotoxicity in animal studies.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk.[3]

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[5]. When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (82-96%, severe 11-45%)[3,4]; onset 1.5 months
	neutropenia (12-19%, severe 2-7%)[3,4]; onset 12 weeks
	thrombocytopenia (70%, severe 4-14%)[3,4]; onset 8 weeks
cardiac	bradycardia/sinus bradycardia (3%)
	palpitation (3-5%)
gastrointestinal	*emetogenic potential: rare*[7]
	flatulence (1-5%)
	gastric hemorrhage (4-6%, severe 1%)
general disorders and administration site conditions	pyrexia (12-15%, severe 1-2%)
infections and infestations	***herpes zoster*** (2-7%, severe 1%)
	tuberculosis (1%)
	urinary tract infections (9-15%, severe 0-2%)[3,4]
injury, poisoning, and procedural complications	***bruising*** (15-27%)[3,4]
investigations	ALT increase (25-28%, severe 1%)
	AST increase (17-20%)[3,4]
	hypercholesterolemia (16-17%)
	weight gain (9-11%, severe 1-2%)
nervous system	dizziness (10-19%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	headache (10-16%)[3,4]
	intracranial hemorrhage (1%, severe 1%)

Adapted from standard reference[3] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
erythromycin[8]	ruxolitinib AUC increased by 27%	moderate CYP 3A4 inhibition by erythromycin	monitor for cytopenias; suggest discontinuing concurrent use if platelets decrease to less than 100 x 10^9/L
fluconazole[8]	predicted increase in ruxolitinib AUC of 100-330% depending on fluconazole dose (based on *in silico* modeling)	dual enzyme inhibition of CYP2C9 and CYP3A4 by fluconazole	suggest 50% dose reduction for ruxolitinib (round up to nearest dosage strength); avoid concurrent use if fluconazole dose >200 mg daily; suggest discontinuing concurrent use if platelets decrease to less than 100 x 10^9/L
ketoconazole[8]	ruxolitinib AUC increased by 91%; ruxolitinib half-life increased to 6 h	strong CYP 3A4 inhibition by ketoconazole	suggest 50% dose reduction for ruxolitinib (round up to nearest dosage strength); monitor for cytopenias; suggest discontinuing concurrent use if platelets decrease to less than 100 x 10^9/L
rifampin[1,4,8]	ruxolitinib AUC decreased by 61-71% and ruxolitinib half-life decreased to 1.7 h; overall pharmacodynamic marker inhibition was reduced by only 10%	CYP 3A4 induction by rifampin	clinical relevance is unclear; avoid concurrent therapy if possible

Ruxolitinib is a major substrate of **CYP 3A4**.[4] Strong CYP 3A4 inhibitors may increase ruxolitinib plasma levels; consider 50% ruxolitinib dose reduction; monitor for cytopenias.[8] Mild to moderate CYP 3A4 inhibitors may increase ruxolitinib plasma levels; monitor for cytopenias.[1,3] Suggest discontinuing concurrent use if platelets decrease to less than 100 x 10^9/L.[8] Grapefruit and grapefruit juice may inhibit CYP 3A4 metabolism of ruxolitinib in the intestinal wall and theoretically may increase ruxolitinib plasma levels[4]; clinical significance is unknown. CYP 3A4 inducers may reduce ruxolitinib plasma levels; avoid concurrent therapy if possible.[1,4]

Ruxolitinib plasma levels may be disproportionately increased when taken concurrently with moderate and strong **dual enzyme inhibitors** (i.e., single agents which inhibit two enzymes such as CYP 3A4 and CYP 2C9 at once). Avoid concurrent use. If concurrent use is unavoidable, consider 50% dose reduction for ruxolitinib (round up to nearest dosage strength). Suggest discontinuing concurrent use if platelets decrease to less than 100 x 10^9/L.[8]

SUPPLY AND STORAGE:

Oral: Novartis Pharmaceuticals Canada Inc. supplies ruxolitinib as 5 mg, 10 mg, 15 mg, and 20 mg tablets. Tablets contain lactose monohydrate. Store at room temperature. Keep in original packaging.[8]

Additional information: Tablets are supplied in blister packaging (4x14 tablets).

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[8-10]

(range 5-25 mg) PO twice daily; see table below.

Administer with food or on an empty stomach.

Starting dose is based on ANC >1 x 10^9/L and platelet count as below:

Platelet ($\times 10^9$/L)	Starting Dose (PO twice daily)	
	Myelofibrosis	**Polycythemia vera**
> 200	20 mg	10 mg
100-200	15 mg	10 mg
50-99	5 mg	5 mg

If unable to swallow tablets, a suspension may be given through a nasogastric tube. Dissolve 1 tablet in ~40 mL water and stir for 10 minutes. Administer within 6 h.[1,4]

Concurrent radiation:

no information found

Dosage in myelosuppression[8-10]*:*

modify according to protocol by which patient is being treated; if no guidelines available, the following adjustments may be used:

- For hemoglobin <80 g/L (for polycythemia vera only): hold until recovery of blood counts; may be restarted at 5 mg PO twice daily and gradually increased based on blood counts.
- For ANC <0.5 x 10^9/L OR Platelets <50 x 10^9/L: hold until recovery of blood counts; may be restarted at 5 mg PO twice daily and gradually increased based on blood counts.

For ANC 0.5 – 1.0 x 10^9/L: modify dose as per table below.

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

EXISTING DOSE (PO twice daily)	NEW DOSE (PO twice daily)		
	Platelet 100-125 (x 10^9/L)	Platelet 75-99 (x 10^9/L)	Platelet 50-74 (x 10^9/L)
25 mg	20 mg	10 mg	5 mg
20 mg	15 mg	10 mg	5 mg
15 mg	15 mg	10 mg	5 mg
10 mg	10 mg	10 mg	5 mg
5 mg	5 mg	5 mg	5 mg

Dosage in renal failure[8-10]*:*

modify according to protocol by which patient is being treated; if no guidelines available, the following adjustments may be used:

Creatinine clearance (mL/min)	Platelet (x 10^9/L)	Starting Dose (PO twice daily)	
		Myelofibrosis	Polycythemia vera
<50	≥100	10 mg	5 mg
	<100	avoid	avoid

Calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{Serum Creatinine in µmol/L}}$

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

Dosage in hepatic failure[8-10]*:*

- for any degree of hepatic impairment and platelets ≥100 x 10^9/L, consider 50% reduction of recommended starting dose based on platelet count (round up to nearest dosage strength)
- avoid in patients with hepatic impairment AND platelets <100 x 10^9/L

Dosage in dialysis[8-10]*:*

peritoneal dialysis or continuous venous hemofiltration: no information found

hemodialysis: give ruxolitinib after dialysis, on day of hemodialysis. Modify according to protocol by which patient is being treated; if no guidelines available, the following adjustments may be used:

Platelet (x 10^9/L)	Starting Dose (Single dose PO after hemodialysis)	
	Myelofibrosis	Polycythemia vera
>200	20 mg	10 mg
100-200	15 mg	10 mg
<100	avoid	avoid

Children:

no information found

REFERENCES:

1. AHFS Drug Information® (database on the Internet). Ruxolitinib phosphate. Lexi-Comp Inc., 2 April 2013. Available at: http://online.lexi.com. Accessed 18 June 2013.
2. Ostojic A, Vrhovac R, Verstovsek S. Ruxolitinib for the treatment of myelofibrosis: its clinical potential. Therapeutics and Clinical Risk Management 2012;8:95-103.
3. Novartis Pharmaceuticals Canada Inc. JAKAVI® product monograph. Dorval, Quebec; 15 June 2012.
4. Lexi-Drugs® (database on the Internet). Ruxolitinib. Lexi-Comp Inc., 3 June 2013. Available at: http://online.lexi.com. Accessed 18 June 2013.
5. Lynda Foltz MD. Personal communication. Hematologist,St.Paul's Hospital; 3 October 2013.
6. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc 2011;86(12):1188-1191.
7. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
8. Novartis Pharmaceuticals Canada Inc. JAKAVI® product monograph. Dorval, Quebec; 19 September 2017.
9. BC Cancer Leukemia/BMT Tumour Group. (ULKPCVRUX) BC Cancer Protocol Summary for Treatment of Polycythemia Vera with Ruxolitinib. Vancouver, British Columbia: BC Cancer; 1 April 2018.
10. BC Cancer Leukemia/BMT Tumour Group. (ULKMFRUX) BC Cancer Protocol Summary for Treatment of Symptomatic Myelofibrosis with Ruxolitinib. Vancouver, British Columbia: BC Cancer; 1 April 2017.