Drug Monograph

A - Drug Name

ruxolitinib

COMMON TRADE NAME(S): Jakavi®

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B - Mechanism of Action and Pharmacokinetics

Ruxolitinib is a Janus kinase (JAK) inhibitor, with selectivity for JAK1 and JAK2 which mediate the signaling of cytokines and growth factors for hematopoiesis and immune function. In myelofibrosis and polycythemia vera, JAK1/2 activity is dysregulated. Ruxolitinib interrupts JAK-STAT signaling and inhibits cell proliferation.

Absorption	Rapidly absorbed; dose proportional pharmacokinetics	
	Bioavailability	95% or greater, no significant effects with food administration
	Peak plasma levels	1 hour
Distribution	Rapidly and widely distributed	
	PPB	97%, mostly to albumin
	Cross blood brain barrier?	No
Metabolism	Metabolized mainly in the liver by CYP3A4, and to a lesser extent by CYP2C9	
	Active metabolites	Yes

Elimination	Urine	74% (< 1% unchanged)
	Feces	22% (< 1% unchanged)
	Half-life	3 hours for ruxolitinib alone
		5.8 hours for ruxolitinib + metabolites

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C - Indications and Status

Health Canada Approvals:

- Myelofibrosis (MF)
- Polycythemia vera (PV)
- Graft-versus-host disease (GVHD)

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

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following side effect information is based on two pivotal phase II studies (COMFORT I and II) and one phase II supporting study involving myelofibrosis (MF) patients. Side effect information specific to polycythemia vera (PV) patients is derived from a pivotal phase III study (RESPONSE) and a supporting phase II study. This table also includes severe or life-threatening adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Angina (4%-MF)	E D
	Bradycardia (3%- MF, 7%-PV)	E
	Endocarditis infective (rare)	E D
	Hypertension (5%-PV)	E D

	Palpitations (5%) (MF)	E
	PR interval prolonged (12%)	E D
	Venous thromboembolism (rare)	E
Gastrointestinal	Constipation (8%-PV)	E D
	Diarrhea (15%-PV)	E D
	Nausea (6%-PV)	E D
	Weight gain (11%-MF, 5%-PV)	E D
General	Fever (15%) (MF)	E
Hematological	Myelosuppression ± infection, bleeding (82%-MF, 44%-PV) (may be severe, includes viral reactivation, opportunistic/atypical infections such as tuberculosis)	E
	Other - Withdrawal/rebound syndrome (MF)	E
Hepatobiliary	↑ LFTs (28%) (MF)	E
Metabolic / Endocrine	Hyperlipidemia (17%-MF, 30%-PV)	E
Musculoskeletal	Musculoskeletal pain (Muscle spasms, back pain) (12%-PV)	E D
Neoplastic	Secondary malignancy (Non-melanoma skin cancers)	E D
Nervous System	Dizziness (19%-MF; 12%-PV)	E
	Headache (16%) (MF)	E
	Leukoencephalopathy (PML) (rare)	E
	Other -Tinnitis (6%-PV)	E D
Respiratory	Cough, dyspnea (10%-PV)	E D

* "*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 ruxolitinib include myelosuppression ± infection, bleeding, hyperlipidemia, ↑ LFTs, dizziness, headache, diarrhea, musculoskeletal pain, weight gain and cough.

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.

Bradycardia and PR interval prolongation have been reported in the phase 3 clinical trials. **Significant QTc increases** were observed with ruxolitinib in a phase 3 clinical trial when compared with best available therapy, but no difference was demonstrated in another clinical trial which compared ruxolitinib to placebo.

Venous thromboembolism (VTE), including fatal cases, has been reported with the use of JAK inhibitors. Based on case reports, there is a possible link between ruxolitinib and VTE; however, patients also had blood disorders that may increase the risk of VTE.

Lipid abnormalities, including increases in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides have been reported. Patients should be monitored and treated according to guidelines.

Increases in systolic pressure by 20 mmHg or more from baseline were reported in some trials but are of unclear significance.

Dose-related myelosuppression can occur, including **anemia, neutropenia and thrombocytopenia**. Median time of onset of myelosuppression is 6 - 12 weeks as observed in the phase 3 trials. Patients with low platelet counts at baseline (< 200 x 10^9/L) are at higher risk of experiencing thrombocytopenia during treatment.

Bleeding events reported in the phase 3 clinical trials include intracranial, gastrointestinal, bruising, epistaxis, post-procedural hemorrhage and hematuria (and may be severe).

Herpes zoster infections have been reported in phase 3 clinical trials. Prompt treatment is required when signs and symptoms of this infection present. **PML** (JC virus) has been reported and may be life-threatening. Ruxolitinib should be held if PML is suspected and discontinued if it is confirmed.

Hepatitis B viral load increases have been reported in patients with chronic HBV infections taking ruxolitinib. These patients should be treated and monitored according to clinical guidelines.

Tuberculosis has been reported, including fatal cases, with patients receiving ruxolitinib.

Visual disorders, including loss of vision, secondary to eye infection is a risk with ruxolitinib. Other severe infections have also been reported, including fungal, as well as sepsis and endocarditis

Withdrawal effects may occur following interruption or discontinuation of ruxolitinib in patients with myelofibrosis, which may include symptoms of myelofibrosis returning, or septic shock-like symptoms within 1 week. Gradual tapering of ruxolitinib should be considered; however, the benefit of this practice is unproven.

Non-Melanoma Skin Cancers (NMSC's), including basal cell, squamous cell, and Merkel cell carcinoma have been reported in patients treated with ruxolitinib, although a causal relationship has not been established. Most of the patients had previous extended hydroxyurea use or pre-malignant skin lesions. Patients are advised to minimize risk factors, such as UV exposure, and periodically examine skin (especially those who have other skin cancer risk factors).

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E - Dosing

Refer to protocol by which 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.

Perform tuberculosis skin test and/or Interferon-gamma release assay before treatment initiation. Caution with interpreting results in severely immunocompromised patients due to possible false negatives.

Starting dose is based on indication, platelet and neutrophil counts, and degree of hepatic or renal impairment.

Treatment should not be started until neutrophils are ≥ 1 x 10^9/L and platelets ≥ 50 x 10^9/L.

Refer to product monograph for GVHD dosing information.

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

Other supportive care:

- Patients should minimize exposure to risk factors for skin cancer such as exposure to sunlight.

Adults:

Starting Dose

ANC (x10^9/L)	Platelet Count (x10^9/L)	Starting Dose Myelofibrosis	Starting Dose Polycythemia vera
> 1	> 200	20 mg PO twice daily	10 mg PO twice daily
> 1	100 - 200	15 mg PO twice daily	10 mg PO twice daily
> 1	75 - 99	10 mg PO twice daily	5 mg PO twice daily
> 1	50 - 74	5 mg PO twice daily	5 mg PO twice daily
≤ 1	< 50	Do not use	Do not use

Titration of Dose

If response to treatment is inadequate (for MF or PV), escalation may proceed as detailed below. The **maximum** dose is 25 mg PO BID.

The starting dose should not be increased during the first 4 weeks of treatment (for patients with MF) and 8 weeks of treatment (for PV).

Discontinue after 6 months if no improvement in symptoms or spleen size (MF) or after 16 months if no clinical benefit (PV).

ANC		Platelets (x 10^9/L)	At 4 weeks (MF), or 8 weeks (PV)	Every 2 weeks (or more) thereafter
>0.75	AND	> 125 (and nadir >100)	↑ by 5mg bid	↑ by 5mg bid, if blood counts criteria are met.
≤0.75	OR	≤ 125 (or nadir < 100)	Do not escalate.	Do not escalate.

Dosage with Toxicity:

MF or PV:

Toxicity (x 10^9/L)	Action
Hb < 80 g/L (PV pts only)	Hold; when Hb recovers, may restart at 5 mg PO twice daily and titrate gradually.
Hb < 120 g/L (PV pts only)	Consider dose reduction, especially if Hb < 100 g/L.
Platelets < 50 or ANC < 0.5	Hold; when platelet and ANC counts above these levels, may restart at 5 mg PO twice daily and titrate gradually.
Platelets 50 to < 125 (MF pts only)	Refer to Dose Modification for Thrombocytopenia table below to minimize holds. May titrate gradually if appropriate.
PML, active tuberculosis, severe infection	Hold and investigate; discontinue if confirmed.
Bleeding requiring intervention (regardless of platelet count)	Hold until event is resolved; consider restart at previous dose if cause of bleeding controlled. If the underlying cause persists, consider restart at a lower dose.

Dose Modification for Thrombocytopenia (MF)

	Dose at Time of Platelet Decline				
Platelet count	**25 mg BID**	**20 mg BID**	**15 mg BID**	**10 mg BID**	**5 mg BID**
	New dose	**New dose**	**New dose**	**New dose**	**New dose**
100 to < 125	20 mg BID	15 mg BID	No change	No change	No change
75 to < 100	10 mg BID	10 mg BID	10 mg BID	No change	No change
50 to < 75	5 mg BID	5 mg BID	5 mg BID	5 mg BID	No change

Dosage with Hepatic Impairment:

Avoid use in patients with hepatic impairment and platelets < 100 x 10^9/L.

Hepatic impairment	Ruxolitinib Dose (MF or PV)
None	No adjustment required.
Any degree	Start at 50% of usual dose*. Monitor carefully and adjust as appropriate.

*round up to the nearest dosage strength, if necessary.

Dosage with Renal Impairment:

Avoid use in patients with moderate to severe renal impairment if platelets < 100 x 10^9/L.

Hemodialysis is not expected to enhance the elimination of ruxolitinib.

Renal Impairment	Ruxolitinib Dose (MF or PV)
Mild	No adjustment required.
Moderate (CrCl 30-50 mL/min)	Start at 50% of usual dose*. Monitor closely for toxicity. Avoid if platelets < 100 x 10^9/L.
Severe (CrCl < 30 mL/min)	
Patients on hemodialysis	Single dose given only after each dialysis session based on platelet count. **MF**: 15 mg for platelets 100-200 x 10^9/L; 20mg for platelets > 200 x 10^9/L **PV**: 10 mg

*round up to the nearest dosage strength, if necessary

Dosage in the elderly:

No dosage adjustments required. No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients with MF or PV.

Dosage based on gender:

Female MF patients may be at a higher risk of anemia than male patients. Ruxolitinib clearance in women with MF was lower compared to men, however, no specific dose adjustment has been recommended.

Children:

Safety and effectiveness of ruxolitinib in pediatric patients with MF or PV have not been established.

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F - Administration Guidelines

- Administer with or without food with a glass of water.
- The tablets should be swallowed whole; do not cut, break, dissolve, crush or chew the tablets.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, skip this dose and take the next dose as scheduled. Do not double the dose to make up for the missed one.
- Store at room temperature (15-25°C).

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Patients who have/had progressive multifocal leukoencephalopathy (PML)

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.
- Ruxolitinib can cause bradycardia and prolongation of PR interval; use with caution in patients on drugs with similar effects or with history of cardiovascular disease including bradycardia, syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure.
- Serious bacterial, mycobacterial, fungal, and viral infections including viral reactivation and opportunistic infections (in some cases fatal) have been reported. Do not administer ruxolitinib in patients with active tuberculosis or active serious infections.
- Contains lactose and should not be used in patients with hereditary lactase/glucose or galactose disorders.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Mutagenicity: No
- Clastogenicity: No
- Teratogenicity: Unknown
- Crosses placental barrier: Yes
- Pregnancy:
  Ruxolitinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose (general recommendation).
- Excretion into breast milk: Documented in animals
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects: Probable

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H - Interactions

Concurrent use of hematopoietic growth factors or cytoreductive agents and ruxolitinib has not been studied.

Monitor more frequently for cytopenias (e.g., twice a week) when starting **a strong CYP3A4 inhibitor** or **combined moderate CYP2C9 and CYP3A4 inhibitors**. Avoid concomitant use if platelet < 100.

Refer to product monograph for management in GVHD.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir)	↑ ruxolitinib concentration and/or toxicity (↑ 91% in AUC)	↓ metabolism of ruxolitinib	For MF and PV, ↓ ruxolitinib by 50% with concomitant use of strong CYP3A4 inhibitors. Monitor for cytopenias. Avoid concomitant use if platelet < 100.
Moderate CYP3A4 inhibitors (e.g., erythromycin, ciprofloxacin, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ ruxolitinib concentration and/or toxicity (↑ 27% in AUC)	↓ metabolism of ruxolitinib	Monitor for cytopenias.
Combined moderate CYP2C9 and CYP3A4 inhibitors (e.g., fluconazole)	↑ ruxolitinib concentration and/or toxicity (↑ 232% in AUC)	↓ metabolism of ruxolitinib	↓ ruxolitinib by 50%; avoid fluconazole doses > 200 mg daily. Monitor for cytopenias. Avoid concomitant use if platelet < 100.
Drugs that decrease heart rate and/or prolong the PR interval (ie. antiarrhythmics, beta blockers, digitalis glycosides, cholinesterase	↑ risk of bradycardia and/or ↑ PR interval	Additive	Avoid if possible.

inhibitors, HIV protease inhibitors, non-dihydropyridine calcium channel blockers)

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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, every 2 - 4 weeks until doses are stabilized, and then as clinically indicated. Monitor more frequently for cytopenias (e.g., twice a week) when starting a strong CYP3A4 inhibitor or combined moderate CYP2C9 and CYP3A4 inhibitors.
Liver and renal function tests	Baseline and as clinically indicated
Lipids (total cholesterol, LDL, triglycerides)	Prior to starting, 4 weeks after starting, then as clinically indicated
Pulse rate and blood pressure	Baseline and as clinically indicated
ECG	Baseline and as clinically indicated
Clinical toxicity assessment for cardiovascular effects, infections (including ocular), bleeding, thrombosis, skin effects (including malignancies) and withdrawal syndrome (if applicable)	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)

- ruxolitinib - For patients with intermediate to high risk symptomatic myelofibrosis, or patients with symptomatic splenomegaly, according to specific criteria
- ruxolitinib - For the treatment of patients with polycythemia vera according to criteria.

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K - References

Harrison C, Kiladjian J, Kathrin Al-Ali H, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366-787-98.

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.

Prescribing information: Jakafi® (ruxolitinib). Incyte Corporation (US), September 2021.

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Summary Safety Review - Xeljanz and Xeljanz XR (tofacitinib), and Jakavi (ruxolitinib) - Janus Kinase (JAK) inhibitors - Health Canada. June 2020.

Tefferi A and Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clinic Proceedings 2011;86(12):1188-91.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.

March 2025 Updated Pregnancy/Lactation section

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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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