JAKAVI in Polycythaemia Vera (PV):

Dosing Guidelines

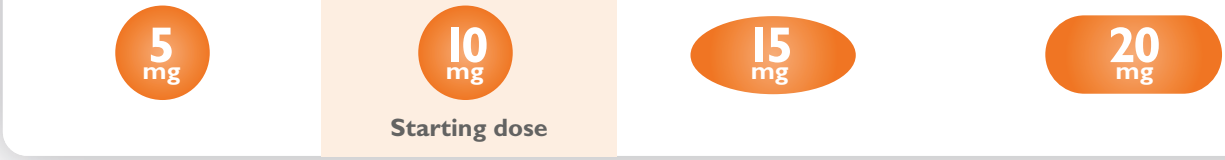
JAKAVI is indicated for the treatment of patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

PLEASE SEE ACCOMPANYING SUMMARY OF PRODUCT CHARACTERISTICS.

JAKAVI®
ruxolitinib

Dose strengths and recommendations

Available strengths of JAKAVI tablets[1]



Tablets shown are not actual size.

Recommended dose[1]

- Starting dose for most patients: 10 mg twice daily (BID)
- Maximum dose: 25 mg BID
- The dose may be modified based on safety, efficacy, and other factors as described on the following pages

Important considerations for starting therapy with JAKAVI[1]

- A blood cell count must be performed before initiating therapy with JAKAVI
  - Complete blood cell counts should be monitored every 2 to 4 weeks until doses are stabilised, and then as clinically indicated
- There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and 100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg BID, and the patients should be titrated cautiously
- The starting dose should not be increased during the first 4 weeks of treatment
  - After 4 weeks, dosing should not be increased more frequently than at 2-week intervals

JAKAVI is to be given orally twice daily.[1]

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Titrate dose based on safety and efficacy considerations

Dose adjustments during treatment by blood count[1]

BLOOD COUNT	DOSE ADJUSTMENT
Platelet count reduced to <100,000/mm^3 during treatment	Consider dose reduction to avoid dose interruption due to thrombocytopaenia
Platelet count reduced to <50,000/mm^3 during treatment or absolute neutrophil count reduced to <500/mm^3 during treatment or haemoglobin reduced to <8 g/dL during treatment	Interrupt treatment. When blood cell counts rise above these levels, restart treatment at 5 mg twice daily. Gradually increase dose as blood cell counts recover based on careful monitoring
Haemoglobin reduced to <12 g/dL during treatment	Consider dose reduction
Haemoglobin reduced to <10 g/dL during treatment	Dose reduction recommended

Dose adjustments based on response to treatment[1]

EFFICACY	DOSE ADJUSTMENT
If efficacy is considered insufficient and blood counts are adequate	Consider increasing dose by a maximum of 5 mg twice daily*

*The starting dose should not be increased during the first 4 weeks of treatment, and thereafter no more frequently than at 2-week intervals. Maximum dose is 25 mg twice daily.[1]

Most haematologic adverse events observed with JAKAVI in PV were Grade 1/2[1,2]

- Haematologic adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopaenia (24.5%)[1]
- Grade 3/4 anaemia was reported in 1.8% of patients, and Grade 3/4 thrombocytopaenia was reported in 5.4% of patients[1]
- Discontinuation for adverse events, regardless of causality, was observed in 3.6% of patients treated with JAKAVI[1,2†]

CTCAE=Common Terminology Criteria for Adverse Events.

†At the time of data cutoff (81 weeks median exposure to therapy in the JAKAVI group).[1,2]

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Dose adjustments for special patient populations

Hepatic impairment[1]

Starting dose

- For PV patients with any hepatic impairment, reduce recommended starting dose by 50%, to be administered twice daily

Monitoring and subsequent doses

- Additional dose modification should be made with careful monitoring of safety and efficacy
- Patients diagnosed with hepatic impairment during therapy with JAKAVI should have complete blood cell counts, including a white blood cell count differential, monitored at least every 1 to 2 weeks for the first 6 weeks after treatment initiation
- Once liver function and blood counts stabilise, complete blood counts should be monitored as clinically indicated
- JAKAVI dose can be titrated to reduce the risk of cytopenia

Renal impairment[1]

Starting dose

- No specific dose adjustment is needed in patients with mild or moderate renal impairment
- For PV patients with severe renal impairment (creatinine clearance <30 mL/min), the recommended starting dose is 5 mg twice daily
- For PV patients with end-stage renal disease (ESRD) on haemodialysis, the recommended starting dose is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis
- Currently no data are available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration

Monitoring and subsequent doses

- Patients should be carefully monitored for safety and efficacy during therapy
- These dose recommendations are based on simulations; any additional dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients

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Additional dose adjustments

Important considerations in dosing[1]

Concomitant use of strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes

- The unit dose of JAKAVI should be reduced by approximately 50%, to be administered twice daily
- More frequent monitoring (eg, twice a week) of haematology parameters and of clinical signs and symptoms of JAKAVI-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes

Older people (≥65 years)

- No additional dose adjustments are recommended for older people

Paediatric population

- The safety and efficacy of JAKAVI in children aged up to 18 years have not been established. No data are available

Pregnancy

- There are no data from the use of JAKAVI in pregnant women
- As a precautionary measure, the use of JAKAVI during pregnancy is contraindicated. Women of childbearing potential should use effective contraception during treatment with JAKAVI

Breast-feeding

- It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk
- JAKAVI must not be used during breast-feeding, and breast-feeding should be discontinued when treatment is started

Fertility

- There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effect on fertility was observed

Driving or operating machinery

- JAKAVI has no or negligible sedating effect. However, patients who experience dizziness should refrain from driving or using machines

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Important Safety Information

JAKAVI® BSS

Important note: Before prescribing, consult full prescribing information.

Presentation: Tablets containing 5 mg, 10 mg, 15 mg, and 20 mg ruxolitinib.

Indications: Treatment of patients with myelofibrosis (MF), including primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. Treatment of patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea.

Dosage: • Perform blood cell count before initiating Jakavi® therapy. Monitor complete blood counts every 2 to 4 weeks until optimal dose is reached. • Administration twice daily at the same time every day, with or without food. • Recommended starting dose for adults in MF: 15 mg (platelet count between 100,000 and 200,000/mm^3) and 20 mg (platelet count >200,000/mm^3) twice daily. • Recommended starting dose for adults in PV: 10 mg twice daily. • Maximum starting dose of 5 mg twice daily in patients with a platelet count <100,000/mm^3, caution in this patient population. • Interrupt treatment if platelet counts <50,000/mm^3 or ANC <500/mm^3 (MF and PV patients) or Hg <8 g/dL (in PV patients). • In PV, dose reduction to be considered if Hg <12 g/dL and recommended if Hg <10 g/dL. • Dose adjustment may be required due to thrombocytopenia or when used with strong CYP3A4 inhibitors or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes (e.g., fluconazole; avoid daily dose of fluconazole >200 mg). • 4 weeks after initiating therapy, dose may be increased at intervals of greater than 2 weeks to ensure adequate response. • Maximum dose is 25 mg twice daily. • Treatment to be continued as long as the benefits outweigh the risks for the patient. • Recommend to reduce the starting dose by approximately 50% in patients with renal impairment (Clcr <30 mL/min) or with hepatic impairment. Monitor patients diagnosed with renal or hepatic impairment and reduce the dose as appropriate. • No dosage adjustment required for elderly patients.

Contraindications: Hypersensitivity to ruxolitinib or to any of the excipients.

Warnings/Precautions: • **Decrease in blood cell count:** Hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia have been reported with Jakavi treatment. Complete blood counts monitoring recommended. Dose reduction or interruption may be required in patients developing thrombocytopenia, anemia and neutropenia. • **Infections:** Treat active serious infections prior to initiating Jakavi therapy. Monitor patients for signs and symptoms of infections during Jakavi treatment, and initiate appropriate treatment for infections. Tuberculosis cases have been reported. Progressive multifocal leukencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. Hepatitis B viral load (HBV-DNA titre) increases have been reported in patients with chronic HBV infections. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. • **Non-Melanoma Skin Cancer (NMSC):** NMSC, including basal cell, squamous cell, and Merkel cell carcinoma, reported in Jakavi treated patients. Periodic skin examination recommended. • **Hepatic and severe renal impairment:** Due to increased Jakavi exposure, dose reduction is required. • **Pregnancy:** Use in pregnancy not recommended. Avoid becoming pregnant during Jakavi therapy. • **Breast-feeding:** Women taking Jakavi should not breast feed.

Interactions: • Caution with CYP3A4 inhibitors or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes. Dose reduction recommended when co-administered with strong CYP3A4 inhibitors or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes. Avoid fluconazole daily doses >200 mg.

Adverse reactions: • **Very common (>10%):** Urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, hypertriglyceridemia, dizziness, headache, alanine aminotransferase increased, aspartate aminotransferase increased, bruising, weight gain. • **Common (1 to 10%):** Herpes zoster, flatulence, constipation, hypertension. • **Uncommon:** Tuberculosis.

Packs and prices: Country specific.

Legal classification: Country specific.

References

BSS, dated May 2015

PLEASE SEE ACCOMPANYING SUMMARY OF PRODUCT CHARACTERISTICS.

JAKAVI® ruxolitinib

JAKAVI dosing in polycythaemia vera

Treatment duration

- Treatment may be continued as long as benefit-risk balance remains positive[1]

Dosing recommendations for JAKAVI differ between PV and myelofibrosis, and dosing should be planned according to the relevant indication.

Summary of dosing in PV

Starting dose: 10 mg BID

Maximum dose: 25 mg BID

References: 1. JAKAVI® (ruxolitinib) tablets: EU Summary of Product Characteristics. Novartis; April 2015. **2.** Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med.* 2015;372(5):426-435.

PLEASE SEE ACCOMPANYING SUMMARY OF PRODUCT CHARACTERISTICS.

NOVARTIS ONCOLOGY

JAKAVI® ruxolitinib

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