

<ul style="list-style-type: none"> • Greater than or equal to $100 \times 10^6/L$ • $50 \times 10^9/L$ to less than $100 \times 10^9/L$ 	<ul style="list-style-type: none"> • 10 mg twice daily • 5 mg once daily
Starting dose for patients with PV:	• 5 mg twice daily
On stable dose for patients with MF or PV:"	
<ul style="list-style-type: none"> • Greater than or equal to 10mg twice daily 	Decrease dose by 50% (round up to the closest available tablet strength)
• 5 mg twice daily	• 5 mg twice daily
• 5 mg once daily	Avoid strong CYP3A4 inhibitor or fluconazole treatment or interrupt Ruxolitinib treatment for the duration of strong CYP3A4 inhibitor or fluconazole use
Starting dose for patients with aGVHD or cGVHD:	
Fluconazole doses of less than or equal to 200 mg	5 mg once daily for patients with aGVHD; 5 mg twice daily for patients with cGVHD
Other CYP3A4 inhibitors	Monitor blood counts more frequently for toxicity and modify the Ruxolitinib dosage for adverse reactions if they occur

5.7 Dose Modifications for Renal or Hepatic Impairment

Moderate to Severe Renal Impairment or End Stage Renal Disease on Dialysis

Modify the Ruxolitinib dosage for patients with moderate (CrCl 30 to 59 mL/min) to severe (CrCl 15 to 29 mL/min) renal impairment or end stage renal disease (ESRD) on dialysis according to Table 10. Avoid use of Ruxolitinib in patients with ESRD (CrCl less than 15 mL/min) not requiring dialysis

Table 10: Dose Modifications for Renal Impairment

Renal Impairment Status	Platelet Count	Recommended starting dosage
Patients with MF		
Moderate or Severe	Greater than 150 × 10 ⁹ /L	No dose Adjustment
	100 to 150 × 10 ⁹ /L	10mg twice daily
	50 to less than 100x10 ⁹ /L	5mg daily
	Less than 50x10 ⁹ /L	Avoid use
ESRD on dialysis	100 to 200 × 10 ⁹ /L	15mg once after dialysis session
	Greater than 200x10 ⁹ /L	20mg once after dialysis session
Patient with PV		
Moderate or Severe	Any	5mg twice daily
ESRD on dialysis	Any	10mg once after dialysis session
Patients with aGVHD		
Moderate or severe	Any	5mg once daily
ESRD on dialysis	Any	5mg once daily after dialysis session
Patients with cGVHD		
Moderate or severe	Any	5mg twice daily
ESRD on dialysis	Any	10mg once after dialysis session

*ESRD= end stage renal disease and CrCl = creatinine clearance

Hepatic Impairment

Modify the Ruxolitinib dosage for patients with hepatic impairment according to table 11

Table 11: Dose Modifications for Hepatic Impairment

Hepatic Impairment status	Platelet Count	Recommended Starting Dosage
Patients with MF Mild, Moderate, or Severe (Child-Pugh Class A, B, C)		
Patients with PV Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Greater than 150 × 10 ⁹ /L 100x10 ⁹ /L to 150x10 ⁹ /L 50 to less than 100x109/L Less than 50x10 ⁹ /L	No dose adjustment 10mg twice daily 5mg daily Avoid Use
	Any	5 mg twice daily
Patients with aGVHD Mild, Moderate, or Severe based on NCI criteria without liver GVHD	Any	No dose adjustment
Stage 1, 2 or 3 Liver aGVHD	Any	No dose adjustment
Stage 4 Liver aGVHD	Any	5 mg once daily
Patients with cGVHD Mild, Moderate, or Severe based on NCI criteria without liver GVHD	Any	No dose adjustment
Stage 4 Liver cGVHD	Any	No dose adjustment
Stage 3 Liver cGVHD	Any	Monitor blood counts more frequently for toxicity and modify the Ruxolitinib dosage for adverse reactions if they occur

5.8 Method of Administration

Ruxolitinib is dosed orally and can be administered with or without food.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

When discontinuing Ruxolitinib therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Ruxolitinib may be considered, for example by 5 mg twice daily each week.

For patients unable to ingest tablets, Ruxolitinib can be administered through a nasogastric tube (8 French or greater) as follows:

- Suspend one tablet in approximately 40 mL of water with stirring for approximately 10 minutes.
 - Within 6 hours after the tablet has dispersed, the suspension can be administered through a nasogastric tube using an appropriate syringe.
- The tube should be rinsed with approximately 75 mL of water. The effect of tube feeding preparations on Ruxolitinib exposure during administration through a nasogastric tube has not been evaluated.

6. CONTRAINDICATIONS

None.

7. WARNINGS AND PRECAUTIONS

7.1 Thrombocytopenia, Anemia and Neutropenia

Treatment with Ruxolitinib can cause thrombocytopenia, anemia and neutropenia.

Manage **thrombocytopenia** by reducing the dose or temporarily interrupting Ruxolitinib. Platelet transfusions may be necessary.

Patients developing **anemia** may require blood transfusions and/or dose modifications of Ruxolitinib.

Severe **neutropenia** (ANC less than 0.5 × 10⁹/L) was generally reversible by withholding Ruxolitinib until recovery.

Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

7.2 Risk of Infection

Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Ruxolitinib until active serious infections have resolved.

Observe patients receiving Ruxolitinib for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

Tuberculosis	<ul style="list-style-type: none">• Tuberculosis infection has been reported in patients receiving Ruxolitinib. Observe patients receiving Ruxolitinib for signs and symptoms of active tuberculosis and manage promptly.• For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Ruxolitinib. The decision to continue Ruxolitinib during treatment of active tuberculosis should be based on the overall risk-benefit determination.
Progressive Multifocal Leukoencephalopathy	Progressive multifocal leukoencephalopathy (PML) has occurred with Ruxolitinib treatment. If PML is suspected, stop Ruxolitinib and evaluate.
Herpes Zoster and Herpes Simplex	<ul style="list-style-type: none">• Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Ruxolitinib.• Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected.• Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Ruxolitinib; patients should be promptly treated and monitored according to clinical guidelines.
Hepatitis B	<ul style="list-style-type: none">• Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Ruxolitinib.• The effect of Ruxolitinib on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

7.3 Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Ruxolitinib
Following discontinuation of Ruxolitinib, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Ruxolitinib: **fever, respiratory distress, hypotension, DIC, or multi-organ failure**. If one or more of these occur after discontinuation of, or while tapering the dose of Ruxolitinib, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Ruxolitinib. Instruct patients not to interrupt or discontinue Ruxolitinib therapy without consulting their physician. When discontinuing or interrupting therapy with Ruxolitinib for reasons other than thrombocytopenia or neutropenia, consider tapering the dose of Ruxolitinib gradually rather than discontinuing abruptly.

7.4 Non-Melanoma Skin Cancer (NMSC)

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Ruxolitinib. Perform periodic skin examinations.

7.5 Lipid Elevations

Treatment with Ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Assess lipid parameters approximately 8-12 weeks following initiation of Ruxolitinib therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

7.6 Major Adverse Cardiovascular Events (MACE)

Clinical trials of another JAK inhibitor in rheumatoid arthritis (a condition for which Ruxolitinib is not indicated) demonstrated an increased risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke, when compared to TNF blockers. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Ruxolitinib particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

7.7 Thrombosis

Clinical trials of another JAK inhibitor in rheumatoid arthritis (not an approved indication for Ruxolitinib) showed increased thrombosis risk (DVT, PE, arterial thrombosis) versus TNF blockers. In Ruxolitinib trials for MF/PV, thromboembolic event rates were comparable to controls. Evaluate and treat promptly if thrombosis symptoms occur. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

7.8 Secondary Malignancies

Clinical trials of another JAK inhibitor in rheumatoid arthritis (not an approved indication for Ruxolitinib) demonstrated increased risk of lymphoma and other malignancies (excluding NMSC) versus TNF blockers, with higher risk in current/past smokers. Weigh benefits against risks before initiating or continuing Ruxolitinib, particularly in patients with known secondary malignancies (excluding treated NMSC), those who develop malignancies, or smokers.

8. ADVERSE REACTIONS

The following are clinically significant adverse reactions:

- Thrombocytopenia, Anemia and Neutropenia
- Risk of Infection
- Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Ruxolitinib
- Non-Melanoma Skin Cancer
- Lipid Elevations
- Major Adverse Cardiovascular Events (MACE)
- Thrombosis

9. DRUG INTERACTIONS

Effect of Other Drugs on Ruxolitinib

Renal Impairment Status	Effect on Ruxolitinib
Fluconazole	<ul style="list-style-type: none">• Concomitant use of with fluconazole increases Ruxolitinib exposure related adverse reactions.• Avoid concomitant use of Ruxolitinib with fluconazole doses of greater than 200 mg daily.• Reduce the Ruxolitinib dosage when used concomitantly with fluconazole doses of less than or equal to 200 mg
Strong CYP3A4 Inhibitors	<ul style="list-style-type: none">• Concomitant use of Ruxolitinib with strong CYP3A4 inhibitors increases its exposure which may increase the risk of exposure related adverse reactions.• Reduce the Ruxolitinib dosage when used concomitantly with strong CYP3A4 inhibitors except in patients with aGVHD or cGVHD
Strong CYP3A4 Inducers	<ul style="list-style-type: none">• Concomitant use of Ruxolitinib with strong CYP3A4 inducers may decrease its exposure which may reduce efficacy of Ruxolitinib.• Monitor patients frequently and adjust the Ruxolitinib dose based on safety and efficacy

10. USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

There are no studies with the use of Ruxolitinib in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown.

10.2 Lactation

Risk Summary

No data is available regarding the presence of Ruxolitinib in human milk, the effects on the breast-fed child, or the effects on milk production. Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Ruxolitinib in human studies, discontinue breastfeeding during treatment with Ruxolitinib and for two weeks after the final dose.

10.3 Pediatric Use

Myelofibrosis

The safety and effectiveness of Ruxolitinib for treatment of myelofibrosis in pediatric patients have not been established.

The safety and effectiveness of Ruxolitinib for treatment of polycythemia vera in pediatric patients have not been established.

Acute Graft-Versus-Host Disease

The safety and effectiveness of Ruxolitinib for treatment of steroid-refractory aGVHD has been established for treatment of pediatric patients 12 years and older. Use of Ruxolitinib in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well- controlled trials of Ruxolitinib in adults and additional pharmacokinetic and safety data in pediatric patients. **The safety and effectiveness of Ruxolitinib for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old.**

Chronic Graft-Versus-Host Disease

The safety and effectiveness of Ruxolitinib for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of pediatric patients 12 years and older. Use of Ruxolitinib in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents and additional pharmacokinetic and safety data in pediatric patients. **The safety and effectiveness of Ruxolitinib for treatment of cGVHD has not been established in pediatric patients younger than 12 years old.**

Other Myeloproliferative Neoplasms, Leukemias, and Solid Tumors

The safety and efficacy of Ruxolitinib in pediatric patients (infants <2 years, children 2-<12 years, and adolescents 12-<17 years) have not been established. Limited data from single-arm trials in relapsed/refractory malignancies and Ph-like ALL showed no new safety signals in these age groups, but clinical benefit was not demonstrated. Juvenile animal studies revealed dose-dependent growth impairment and bone toxicity at exposures below the maximum recommended human dose, warranting careful risk-benefit consideration for pediatric use, particularly with long-term therapy.

10.4 Geriatric Use

In myelofibrosis (MF) trials, 52% of patients were ≥65 years (15% ≥75 years), with no clinically meaningful differences in safety or efficacy compared to younger patients. For acute GVHD, insufficient numbers of elderly patients were studied to assess differential effects. In chronic GVHD trials, 11% of patients were ≥65 years, with no significant safety or effectiveness variations observed versus younger patients.

10.5 Renal Impairment

Total exposure of Ruxolitinib and its active metabolites increased with moderate (CrCl 30 to 59 mL/min) and severe (CrCl 15 to 29 mL/min) renal impairment, and ESRD (CrCl less than 15 mL/min) on dialysis. Modify Ruxolitinib dosage as recommended.

10.6 Hepatic Impairment

Exposure of Ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.

Reduce Ruxolitinib dosage as recommended in patients with MF or PV with hepatic impairment. Reduce dosage as recommended for patients with Stage 4 liver aGVHD.

Monitor blood counts more frequently for toxicity and modify the Ruxolitinib dosage for adverse reactions if they occur for patients with Score 3 liver cGVHD.

11. OVERDOSAGE

There is no known antidote for overdoses with Ruxolitinib. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia.

Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Ruxolitinib.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ruxolitinib is a kinase inhibitor that targets JAK1 and JAK2, blocking cytokine signaling critical for hematopoiesis and immune responses. By inhibiting JAK-STAT pathway activation, it reduces aberrant signaling in myeloproliferative neoplasms (MF/PV) and mitigates inflammatory cytokine production (e.g., TNF-α, IL-6) implicated in GVHD pathogenesis. Preclinical models demonstrate reduced splenomegaly (MF/PV) and decreased immune-cell infiltration (GVHD)

12.2 Pharmacodynamics

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from patients with MF and PV. STAT3 phosphorylation reached maximal inhibition 2 hours after Ruxolitinib dosing and returned to near baseline by 10 hours in patients with MF and PV.

Cardiac Electrophysiology

At a dose of 1.25 to 10 times the highest recommended starting dosage, Ruxolitinib does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Mean Ruxolitinib maximal plasma concentration (Cmax) and AUC increased proportionally over a single dose range of 5 mg to 200 mg (4 times the approved highest recommended total daily dosage of 25 mg twice daily). Mean Ruxolitinib Cmax ranged from 205 nM to 7100 nM and AUC ranged from 862 nM*hr to 30700 nM*hr over a single dose range of 5 mg to 200 mg.

Absorption

Ruxolitinib achieves Cmax within 1 hour to 2 hours post-dose. Oral absorption of Ruxolitinib is estimated to be at least 95%.

Effect of Food

No clinically relevant changes in the pharmacokinetics of Ruxolitinib were observed upon administration of Ruxolitinib with a high-fat, high-calorie meal (approximately 800 to 1000 calories of which 50% were derived from fat).

Distribution

The mean Ruxolitinib volume of distribution at steady-state is 72 L (coefficient of variation [CV] 29%) in patients with MF and 75 L (23%) in patients with PV.

Protein binding of Ruxolitinib is approximately 97%, mostly to albumin.

Elimination

The mean elimination half-life of Ruxolitinib is approximately 3 hours and the mean elimination half-life of Ruxolitinib and its metabolites is approximately 5.8 hours in healthy volunteers.

Ruxolitinib clearance (%CV) was 17.7 L/h in women and 22.1 L/h in men with MF (39%).

Ruxolitinib clearance (%CV) was 12.7 L/h (42%) in patients with PV.

Ruxolitinib clearance (%CV) was 11.8 L/h (63%) in patients with aGVHD.

Ruxolitinib clearance (%CV) was 9.7 L/h (51%) in patients with cGVHD.

Metabolism

Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9.

Excretion

Following a single oral dose of radiolabeled Ruxolitinib, 74% of radioactivity was excreted in urine and 22% via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity.

Specific Populations

No clinically relevant differences in Ruxolitinib pharmacokinetics were observed based on age (12-73 years), race (White, Asian), sex, or weight (29-139 kg).

Patients with Renal Impairment

Total AUC of Ruxolitinib and its active metabolites increased by 1.3-, 1.5-, 1.9-, and 1.6-fold in subjects with mild, moderate, severe renal impairment, and with ESRD after dialysis, respectively, compared to subjects with normal renal function (CrCl ≥ 90 mL/min).

The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure with renal impairment. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out.

Patients with Hepatic Impairment

In patients with acute or chronic GVHD, mild to severe hepatic impairment (NCI criteria) did not clinically affect Ruxolitinib pharmacokinetics. However, in non-GVHD populations, AUC increased up to 1.9-fold (Child-Pugh A/B/C) versus normal hepatic function. pSTAT3 inhibition generally correlated with exposure, though prolonged pharmacodynamic activity was observed in some severe hepatic impairment cases despite plasma concentrations.

Patients with Liver Involvement in Graft-Versus-Host Disease

No clinically relevant effect on Ruxolitinib pharmacokinetics was observed based on Stage 1, 2 or 3 liver aGVHD, or Score 1, or 2 liver cGVHD.

A lower apparent clearance of Ruxolitinib was observed in patients with Stage 4 liver aGVHD compared to patients with no liver aGVHD.

The effect of Score 3 liver cGVHD on the pharmacokinetics of Ruxolitinib is unknown.

13. PHARMACEUTICAL PARTICULARS

13.1 Pack Size

For 5mg and 15mg tablets

4x 14's (6) tablets.

Alu/PVDC blisters having 14 tablets in blister and packed in unit carton with leaflet.

13.2 Storage Conditions

Store below 30°C.

Protect from sunlight and moisture.

13.3 Dosage & Instructions

As directed by physician.

Keep out of reach of children.

خوراک : ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایت : دو اکو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچنے سے دور رکھیں۔

For adverse event reporting, kindly email us at

pharmacovigilance@oncogenpharma.com.pk

14. MANUFACTURER



Oncogen Pharma (Pvt.) Limited.

Plot No: WH-26 & 27-A3, Korangi Creek Industrial Park (KCIP), Karachi 75190, Pakistan.

www.oncogenpharma.com.pk