Ruxotor
Ruxolitinib Phosphate INN

Everest

COMPOSITION

Ruxotor 5 Tablet: Each film coated tablet contains Ruxolitinib Phosphate INN equivalent to Ruxolitinib 5 mg
Ruxotor 10 Tablet: Each film coated tablet contains Ruxolitinib Phosphate INN equivalent to Ruxolitinib 10 mg

PHARMACOLOGY

Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.
MF and PV are myeloproliferative neoplasms (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. In a mouse model of JAK2V617F-positive MPN, oral administration of Ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen and decreased circulating inflammatory cytokines (e.g., TNF-α, IL-6).
JAK-STAT signaling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GVHD pathogenesis. In a mouse model of aGVHD, oral administration of Ruxolitinib was associated with decreased expression of inflammatory cytokines in colon homogenates and reduced immune-cell infiltration in the colon.

INDICATION

Ruxolitinib is a kinase inhibitor indicated for treatment of:
• Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults.
• Polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea.
• Pteroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older.
• Chronic graft-versus-host disease after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

DOSAGE AND ADMINISTRATION

Monitoring to Assess Safety Prior to Ruxolitinib treatment:
• Perform a complete blood count
• Inquire about past infections, including tuberculosis, herpes simplex, herpes zoster, and hepatitis B
During treatment with Ruxolitinib:
• Perform a complete blood count every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
• Assess lipid parameters approximately 8-12 weeks following initiation of Ruxolitinib therapy.

Recommended Dosage for Myelofibrosis

The recommended starting dose of Ruxolitinib is based on platelet count (Table 1). Doses may be titrated based on safety and efficacy.
Table 1: Ruxolitinib Starting Doses for Myelofibrosis

Platelet Count	Starting Dose
Greater than 200 × 10^9/L	20 mg orally twice daily
100 × 10^9/L to 200 × 10^9/L	15 mg orally twice daily
50 × 10^9/L to less than 100 × 10^9/L	5 mg orally twice daily

Dose Modification Guidelines for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 × 10^9/L or Greater

Treatment Interruption and Restarting Dosing
Interrupt treatment for platelet counts less than 50 × 10^9/L or absolute neutrophil count (ANC) less than 0.5 × 10^9/L.
After recovery of platelet counts above 50 × 10^9/L and ANC above 0.75 × 10^9/L, dosing may be restarted. Table 2 illustrates the maximum allowable dose that may be used in restarting Ruxolitinib after a previous interruption.
Table 2: Myelofibrosis: Maximum Restarting Doses for Ruxolitinib after Safety Interruption for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 × 10^9/L or Greater

Current Platelet Count	Maximum Dose When Restarting Ruxolitinib Treatment*
Greater than or equal to 125 × 10^9/L	20 mg twice daily
100 to less than 125 × 10^9/L	15 mg twice daily
75 to less than 100 × 10^9/L	10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
50 to less than	5 mg twice daily for at least 2 weeks;
75 × 10^9/L	If stable, may increase to 10 mg twice daily
Less than 50 × 10^9/L	Continue hold

Maximum doses are displayed. When restarting, begin with a dose at least 5 mg twice daily below the dose at interruption.
Following treatment interruption for ANC below 0.5 × 10^9/L, after ANC recovers to 0.75 × 10^9/L or greater, restart dosing at the higher of 5 mg once daily or 5 mg twice daily below the largest dose in the week prior to the treatment interruption.

Dose Reductions
Dose reductions should be considered if the platelet counts decrease as outlined in Table 3 with the goal of avoiding dose interruptions for thrombocytopenia.

Table 3: Myelofibrosis: Dosing Recommendations for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 × 10^9/L or Greater

	Dose at Time of Platelet Decline				
Platelet Count	25 mg twice daily	20 mg twice daily	15 mg twice daily	10 mg twice daily	5 mg twice daily
	New Dose	New Dose	New Dose	New Dose	New Dose
100 to less than 125 × 10^9/L	20 mg twice daily	15 mg twice daily	No Change	No Change	No Change
75 to less than 100 × 10^9/L	10 mg twice daily	10 mg twice daily	10 mg twice daily	No Change	No Change
50 to less than 75 × 10^9/L	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No Change
Less than 50 × 10^9/L	Hold	Hold	Hold	Hold	Hold

Dose Modification Based on Insufficient Response for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 × 10^9/L or Greater

If the response is insufficient and platelet and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks.
Consider dose increases in patients who meet all of the following conditions:
1. Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% reduction in spleen volume as measured by computed tomography (CT) or magnetic resonance imaging (MRI);
2. Platelet count greater than 125 × 10^9/L at 4 weeks and platelet count never below 100 × 10^9/L;
3. ANC Levels greater than 0.75 × 10^9/L.

Based on limited clinical data, long-term maintenance at a 5 mg twice daily dose has not shown responses and continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks. Discontinue Ruxolitinib if there is no spleen size reduction or symptom improvement after 6 months of therapy.

Dose Modifications for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with Platelet Counts of 50 × 10^9/L to Less Than 100 × 10^9/L

This section applies only to patients with platelet counts of 50 × 10^9/L to less than 100 × 10^9/L prior to any treatment with Ruxolitinib. See dose modifications in (Dose Modification Guidelines for Hematological Toxicity for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 × 10^9/L or Greater) for hematological toxicity in patients whose platelet counts were 100 × 10^9/L or more prior to starting treatment with Ruxolitinib.

Treatment Interruption and Restarting Dosing
Interrupt treatment for platelet counts less than 25 × 10^9/L or ANC less than 0.5 × 10^9/L.
After recovery of platelet counts above 35 × 109/L and ANC above 0.75 × 10^9/L, dosing may be restarted. Restart dosing at the higher of 5 mg once daily or 5 mg twice daily below the largest dose in the week prior to the decrease in platelet count below 25 × 10^9/L or ANC below 0.5 × 10^9/L that led to dose interruption.

Dose Reductions
Reduce the dose of Ruxolitinib for platelet counts less than 35 × 10^9/L as described in Table 4.
Table 4: Myelofibrosis: Dosing Modifications for Thrombocytopenia for Patients with Starting Platelet Count of 50 × 10^9/L to Less Than 100 × 10^9/L

Platelet Count	Dosing Recommendations
Less than 25 × 10^9/L	Interrupt dosing.
25 × 10^9/L to less than 35 × 10^9/L and the platelet count decline is less than 20% during the prior four weeks	Decrease dose by 5 mg once daily. For patients on 5 mg once daily, maintain dose at 5 mg once daily.
25 × 10^9/L to less than 35 × 10^9/L and the platelet count decline is 20% or greater during the prior four weeks	Decrease dose by 5 mg twice daily. For patients on 5 mg twice daily, decrease the dose to 5 mg once daily. For patients on 5 mg once daily, maintain dose at 5 mg once daily.

Dose Modifications Based on Insufficient Response for Patients with Myelofibrosis and Starting Platelet Count of 50 × 10^9/L to Less Than 100 × 10^9/L

Do not increase doses during the first 4 weeks of therapy, and do not increase the dose more frequently than every 2 weeks.
If the response is insufficient as defined in (Dose Modification Based on Insufficient Response with Myelofibrosis Starting Treatment with a platelet count of 100 × 10^9/L or Greater), doses may be increased by increments of 5 mg daily to a maximum of 10 mg twice daily if:
1.the platelet count has remained at least 40 × 10^9/L, and
2.the platelet count has not fallen by more than 20% in the prior 4 weeks, and
3.the ANC is more than 1 × 10^9/L, and
4.the dose has not been reduced or interrupted for an adverse event or hematological toxicity in the prior 4 weeks.
Continuation of treatment for more than 6 months should be limited to patients in whom the benefits outweigh the potential risks. Discontinue Ruxolitinib if there is no spleen size reduction or symptom improvement after 6 months of therapy.

Dose Modification for Bleeding

Interrupt treatment for bleeding requiring intervention regardless of current platelet count. Once the bleeding event has resolved, consider resuming treatment at the prior dose if the underlying cause of bleeding has been controlled. If the bleeding event has resolved but the underlying cause persists, consider resuming treatment with Ruxolitinib at a lower dose.

Recommended Dosage for Polycythemia Vera

The recommended starting dose of Ruxolitinib is 10 mg twice daily. Doses may be titrated based on safety and efficacy.

Dose Modification Guidelines for Patients with Polycythemia Vera

Dose Reductions
Dose reductions should be considered for hemoglobin and platelet count decreases as described in Table 5.
Table 5: Polycythemia Vera: Dose Reductions

Hemoglobin and/or Platelet Count	Dosing Recommendations
Hemoglobin greater than or equal to 12 g/dL and platelet count greater than or equal to 100 × 10^9/L	No change required.
Hemoglobin 10 to less than 12 g/dL and platelet count 75 to less than 100 × 10^9/L	Dose reductions should be considered with the goal of avoiding dose interruptions for anemia and thrombocytopenia.
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 × 10^9/L	Reduce dose by 5 mg twice daily. For patients on 5 mg twice daily, decrease the dose to 5 mg once daily.
Hemoglobin less than 8 g/dL or platelet count less than 50 × 10^9/L	Interrupt dosing.

Treatment Interruption and Restarting Dosing
Interrupt treatment for hemoglobin less than 8 g/dL, platelet counts less than 50 × 10^9/L or ANC less than 1.0 × 10^9/L.
After recovery of the hematologic parameter(s) to acceptable levels, dosing may be restarted.

Table 6 illustrates the dose that may be used in restarting Ruxolitinib after a previous interruption.
Table 6: Polycythemia Vera: Restarting Doses for Ruxolitinib after Safety Interruption for Hematologic Parameter(s)
Use the most severe category of a patient's hemoglobin, platelet count, or ANC abnormality to determine the corresponding maximum restarting dose.

Hemoglobin, Platelet Count, or ANC	Maximum Restarting Dose
Hemoglobin less than 8 g/dL OR platelet count less than 50 × 10^9/L OR ANC less than 1 × 10^9/L	Continue hold
Hemoglobin 8 to less than 10 g/dL or platelet count 50 to less than 75 × 10^9/L OR ANC 1 to less than 1.5 × 10^9/L	5 mg twice daily or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin 10 to less than 12 g/dL or platelet count 75 to less than 100 × 10^9/L OR ANC 1.5 to less than 2 × 10^9/L	10 mg twice daily or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin greater than or equal to 12 g/dL OR platelet count greater than or equal to 100 × 10^9/L OR ANC greater than or equal to 2 × 10^9/L	15 mg twice daily or no more than 5 mg twice daily less than the dose which resulted in dose interruption

Patients who had required dose interruption while receiving a dose of 5 mg twice daily, may restart at a dose of 5 mg twice daily or 5 mg once daily, but not higher, once hemoglobin is greater than or equal to 10 g/dL, platelet count is greater than or equal to 75 × 10^9/L, and ANC is greater than or equal to 1.5 × 10^9/L.

Dose Management after Restarting Treatment
After restarting Ruxolitinib following treatment interruption, doses may be titrated, but the maximum total daily dose should not exceed 5 mg less than the dose that resulted in the dose interruption. An exception to this is dose interruption following phlebotomy-associated anemia, in which case the maximal total daily dose allowed after restarting Ruxolitinib would not be limited.

Dose Modifications Based on Insufficient Response for Patients with Polycythemia Vera
If the response is insufficient and platelet, hemoglobin, and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every two weeks.
Consider dose increases in patients who meet all of the following conditions:
1.Inadequate efficacy as demonstrated by one or more of the following:
a.Continued need for phlebotomy
b.WBC greater than the upper limit of normal range
c. Platelet count greater than the upper limit of normal range
d. Palpable spleen that is reduced by less than 25% from Baseline
2. Platelet count greater than or equal to 140 × 10^9/L
3. Hemoglobin greater than or equal to 12 g/dL
4. ANC greater than or equal to 1.5 × 10^9/L

Recommended Dosage for Acute Graft-Versus-Host Disease

The recommended starting dose of Ruxolitinib is 5 mg given orally twice daily. Consider increasing the dose to 10 mg twice daily after at least 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with Ruxolitinib.
Consider tapering Ruxolitinib after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper Ruxolitinib by one dose level approximately every 8 weeks (10 mg twice daily to 5 mg twice daily to 5 mg once daily). If aGVHD signs or symptoms recur during or after the taper of Ruxolitinib, consider retreatment.

Dose Modification Guidelines for Patients with Acute Graft-Versus-Host Disease

Monitor complete blood counts (CBC), including platelet count and ANC, and bilirubin prior to initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as indicated clinically.

Table 7: Dose Modifications for Adverse Reactions in Patients with Acute GVHD

Laboratory Parameter	Dosing Recommendations
Clinically significant thrombocytopenia after supportive measures	Reduce dose by 1 dose level. When platelets recover to previous values, dosing may return to prior dose level.
ANC less than 1 × 10^9/L considered related to Ruxolitinib	Hold Ruxolitinib for up to 14 days; resume at 1 dose level lower upon recovery.

Laboratory Parameter	Dosing Recommendations
Total Bilirubin elevation, no liver GVHD	3.0-5.0 × ULN: Continue Ruxolitinib at 1 dose level lower until recovery. > 5.0-10.0 × ULN: Hold Ruxolitinib for up to 14 days until bilirubin ≤ 1.5 × ULN; resume at current dose upon recovery. Total bilirubin > 10.0 × ULN: Hold Ruxolitinib for up to 14 days until bilirubin ≤1.5×ULN;resume at 1 dose level lower upon recovery.
Total Bilirubin elevation, liver GVHD	> 3.0 × ULN: Continue Ruxolitinib at 1 dose level lower until recovery.

Recommended Dosage for Chronic Graft-Versus-Host Disease
The recommended starting dose of Ruxolitinib is 10 mg given orally twice daily.
Consider tapering Ruxolitinib after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper Ruxolitinib by one dose level approximately every 8 weeks (10 mg twice daily to 5 mg twice daily to 5 mg once daily). If GVHD signs or symptoms recur during or after the taper of Ruxolitinib, consider retreatment.

Dose Modification Guidelines for Patients with Chronic Graft-Versus-Host Disease
Monitor complete blood counts (CBC), including platelet count and ANC, and bilirubin prior to initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as indicated clinically.
Modify the dose of Ruxolitinib for adverse reactions as described in Table 8. For dose reductions, patients who are currently receiving Ruxolitinib 10 mg twice daily may have their dose reduced to 5 mg twice daily; patients receiving 5 mg twice daily may have their dose reduced to 5 mg once daily. Patients who are unable to tolerate Ruxolitinib at a dose of 5 mg once daily should have treatment interrupted until their clinical and/or laboratory parameters recover.
Table 8: Dose Modifications for Adverse Reactions in Patients with Chronic GVHD

Parameter	Dosing Recommendations
Platelet count less than 20 × 10^9/L	Reduce Ruxolitinib by 1 dose level. If resolved within 7 days, dosing may return to initial dose level. If not resolved within 7 days, then maintain at 1 dose level lower.
ANC less than 0.75 × 10^9/L considered related to Ruxolitinib	Reduce Ruxolitinib by 1 dose level; resume at initial dose level upon recovery.
ANC less than 0.5 × 10^9/L considered related to Ruxolitinib	Hold Ruxolitinib for up to 14 days; resume at 1 dose level lower upon recovery. May resume initial dose level when ANC greater than 1.0 × 10^9/L.
Total Bilirubin: 3.0-5.0 × ULN	Continue Ruxolitinib at 1 dose level lower until recovery. If resolved within 14 days, then increase by one dose level. If not resolved within 14 days, then maintain the decreased dose level.
Total Bilirubin: > 5.0-10.0 × ULN	Hold Ruxolitinib for up to 14 days until resolved; resume at current dose upon recovery. If not resolved within 14 days, then resume at 1 dose level lower upon recovery.
Total Bilirubin: > 10.0 × ULN	Hold Ruxolitinib for up to 14 days until resolved; resume at 1 dose level lower upon recovery. If not resolved within 14 days, discontinue.
Other Adverse Reactions: Grade 3	Continue Ruxolitinib at 1 dose level lower until recovery.
Other Adverse Reactions: Grade 4	Discontinue Ruxolitinib.

Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole
Modify the Ruxolitinib dosage when coadministered with strong CYP3A4 inhibitors or doses of less than or equal to 200 mg of Fluconazole, according to Table 9. Avoid concomitant use of Ruxolitinib with Fluconazole doses of greater than 200 mg daily.
Table 9: Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

For patients coadministered strong CYP3A4 inhibitors or doses of less than or equal to 200 mg of Fluconazole	Recommended Ruxolitinib Dose Modification
Starting dose for patients with MF with a platelet count:	
Greater than or equal to 100 × 10^9/L	10 mg twice daily
50 × 109/L to less than 100 × 10^9/L	5 mg once daily
Starting dose for patients with PV:	5 mg twice daily
If on stable dose for patients with MF or PV:	
Greater than or equal to 10 mg twice daily	Decrease dose by 50% (round up to the closest available tablet strength)
5 mg twice daily	5 mg once 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.

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 (CLcr 30 to 59 mL/min) to severe (CLcr 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 (CLcr 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	10 mg twice daily
	50 to less than 100 × 10^9/L	5 mg daily
	Less than 50 × 10^9/L	Avoid use
ESRD on dialysis	100 to 200 × 10^9/L	15 mg once after dialysis session
	Greater than 200 × 10^9/L	20 mg once after dialysis session
Patients with PV		
Moderate or Severe	Any	5 mg twice daily
	Any	10 mg once after dialysis session
Patients with aGVHD		
Moderate or Severe	Any	5 mg once daily
	Any	5 mg once after dialysis session
Patients with cGVHD		
Moderate or Severe	Any	5 mg twice daily
	Any	10 mg once after dialysis session

ESRD = end stage renal disease and CLcr = 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)	Greater than 150 × 10^9/L	No dose adjustment
	100 × 10^9/L to 150 × 10^9/L	10 mg twice daily
	50 to less than 100 × 10^9/L	5 mg daily
	Less than 50 × 10^9/L	Avoid use
	Platelet Count	Recommended Starting Dosage
	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	No dose adjustment

Patients with cGVHD		
Mild, Moderate, or Severe based on NCI criteria without liver GVHD	Any	No dose adjustment
Score 1 or 2 Liver cGVHD	Any	No dose adjustment
Score 3 Liver cGVHD	Any	Monitor blood counts more frequently for toxicity and modify the Ruxolitinib dosage for adverse reactions if they occur.

CONTRAINDICATION
None.

ADVERSE REACTION
- 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
- Secondary Malignancies

WARNINGS AND PRECAUTION
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 × 10^9/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.

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. Some of the infections reported were: Tuberculosis, Progressive Multifocal Leukoencephalopathy, Herpes Zoster and Herpes Simplex and Hepatitis B.

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.

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.

Lipid Elevations
Treatment with Ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Ruxolitinib. Assess lipid parameters approximately 8-12 weeks following initiation of Ruxolitinib therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

Major Adverse Cardiovascular Events (MACE)
Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Ruxolitinib is not indicated. 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.

Thrombosis
Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Ruxolitinib is not indicated. In patients with MF and PV treated with Ruxolitinib in clinical trials, the rates of thromboembolic events were similar in Ruxolitinib and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Secondary Malignancies
Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Ruxolitinib is not indicated. Patients who are current or past smokers are at additional increased risk.
Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Ruxolitinib, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers

USE IN SPECIFIC POPULATIONS
Pregnancy: Ruxolitinib caused adverse developmental outcomes in animal studies at high doses associated with maternal toxicity, including reduced fetal weight and late resorptions. There are no adequate studies in pregnant women. The background risk of birth defects and miscarriage in the general population is 2–4% and 15–20%, respectively. Avoid use in pregnancy unless necessary.
Lactation: Breastfeeding should be discontinued during treatment and for two weeks after the final dose.
Pediatric Use: Ruxolitinib is effective for steroid-refractory aGVHD and cGVHD in patients ≥12 years but unestablished for children aged less than 12 years.
Geriatric Use: In clinical studies, 52% of myelofibrosis patients and 11% of cGVHD patients were ≥65 years. No significant differences in safety or efficacy were observed between older and younger patients. For aGVHD, insufficient data are available to assess differences in response between elderly and younger populations.
Renal Impairment: Total exposure of Ruxolitinib and its active metabolites increased with moderate (CLcr 30 to 59 mL/min) and severe (CLcr 15 to 29 mL/min) renal impairment, and ESRD (CLcr less than 15 mL/min) on dialysis. Modify Ruxolitinib dosage as recommended.
Hepatic Impairment: Reduce Ruxolitinib dosage as recommended in patients with MF or PV with hepatic impairment. Reduce Ruxolitinib 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.

Overdose
There is no antidote for Ruxolitinib overdose. High doses cause myelosuppression (leukopenia, anemia, thrombocytopenia). Supportive treatment is recommended. Hemodialysis does not enhance elimination. Single 200 mg doses showed acceptable acute tolerability.

PHARMACEUTICAL INFORMATION
Storage
Store below 30° C in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied
Ruxotor 5 tablet: Each HDPE container contains 60 tablets (each film coated tablet contains Ruxolitinib Phosphate INN equivalent to Ruxolitinib 5 mg), a silica gel desiccant and polyester coil with child resistant closure.
Ruxotor 10 tablet: Each HDPE container contains 60 tablets (each film coated tablet contains Ruxolitinib Phosphate INN equivalent to Ruxolitinib 10 mg), a silica gel desiccant and polyester coil with child resistant closure.

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