141.0 mm

206.0 mm

Mylonib Tablet
(Ruxolitinib)

مائلونیب ٹیبلیٹ
(روکسولی ٹینیب)

COMPOSITION

Mylonib Tablet 5mg
Each tablet contains:
Ruxolitinib as phosphate……..5mg
(Innovator's Specifications)

Mylonib Tablet 15mg
Each tablet contains:
Ruxolitinib as phosphate……..15mg
(Innovator's Specifications)

Mylonib Tablet 20mg
Each tablet contains:
Ruxolitinib as phosphate……..20mg
(Innovator's Specifications)

DESCRIPTION

Ruxolitinib is an anticancer drug and a Janus kinase (JAK) inhibitor. It is a potent and selective inhibitor of JAK1 and JAK2, which are tyrosine kinases involved in cytokine signalling and hematopoiesis.

MECHANISM OF ACTION

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.

INDICATIONS

Myelofibrosis

Ruxolitinib is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia Vera MF and post-essential thrombocythemia MF in adults.

Polycythemia Vera

Ruxolitinib is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

Acute Graft-Versus-Host Disease

Ruxolitinib is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older.

Chronic Graft-Versus-Host Disease

Ruxolitinib is indicated for treatment of chronic graft-versus-host disease (aGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

DOSAGE & ADMINISTRATION

A. Myelofibrosis

The recommended starting dose of Ruxolitinib is based on platelet count (Table 1). A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Doses may be titrated based on safety and efficacy.

Table 1: Ruxolitinib Starting Doses for Myelofibrosis

Platelet Count	Starting Dose
Greater than 200 × 109/L	20 mg orally twice daily
100 × 109/L to 200 × 109/L	15 mg orally twice daily
50 × 109/L to less than 100 × 109/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 × 109/L	20 mg twice daily
100 to less than 125 × 109/L	15 mg twice daily
75 to less than 100 × 109/L	10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
50 to less than 75 × 109/L	5 mg twice daily for at least 2 weeks; if stable, may increase to 10 mg twice daily
Less than 50 × 109/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 new dose	20 mg twice daily new dose	15 mg twice daily new dose	10 mg twice daily new dose	5 mg twice daily 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:

a. 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);

b. Platelet count greater than 125 × 10^9/L at 4 weeks and platelet count never below 100 × 10^9/L;

c. 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 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 × 10^9/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 × 109/L to Less Than 100 × 10^9/L

Platelet Count	Dosing Recommendations
Less than 25 × 1 09/L	• Interrupt dosing.
25 × 109/L to less than 35 × 109/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 × 109/ L to less than 35 × 109/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, doses may be increased by increments of 5 mg daily to a maximum of 10 mg twice daily if:

a) The platelet count has remained at least 40 × 10^9/L, and

b) The platelet count has not fallen by more than 20% in the prior 4 weeks, and

c) The ANC is more than 1 × 10^9/L, and

d) 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.

B. 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

A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated

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 × 109/L	• No change required.
Hemoglobin 10 to less than 12 g/dlAND platelet count 75 to less than 100 × 109/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 × 109/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 × 109/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 × 109/L OR ANC less than 1 × 109/L	Continue hold
Hemoglobin 8 to less than 10 g/dl OR platelet count 50 to less than 75 × 109/L OR ANC 1 to less than 1.5 × 109/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 × 109/L OR ANC 1.5 to less than 2 × 109/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 × 109/L OR ANC greater than or equal to 2 × 109/L	15 mg twice daily* or no more than 5 mg twice daily less than the dose which resulted in dose interruption

*Continue treatment for at least 2 weeks; if stable, may increase dose by 5 mg twice aily.

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.

C.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. Modify the dose of Ruxolitinib for adverse reactions as described in Table 7. 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 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 × 109/L considered related to Ruxolitinib	Hold Ruxolitinib for up to 14 days; resume at 1 dose level lower upon recovery.
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.

D.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 × 109/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 × 109/L considered related to Ruxolitinib ANC less than 0.5 × 109/L considered related to Ruxolitinib	Reduce Ruxolitinib by 1 dose level; resume at initial dose Level upon recovery. 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 × 109/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. 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: 5.0 - 10.0 × ULN	
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 .

E. Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

Modify the Ruxolitinib dosage when co administered 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 co administered 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 × 109/L	10 mg twice daily
• 50 × 109/L to less than 100 × 109/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

F. 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 × 109/L	No dose adjustment
	100 to 150 × 109/L	10 mg twice daily
	50 to less than 100 × 109/L	5 mg daily
	Less than 50 × 109/L	Avoid use
ESRD on dialysis	100 to 200 × 109/L	15 mg once after dialysis session
	Greater than 200 × 109/L	20 mg once after dialysis session
Patients with PV		
Moderate or Severe	Any	5 mg twice daily
ESRD on dialysis	Any	10 mg once after dialysis session
Patients with aGVHD		
Moderate or Severe	Any	5 mg once daily
ESRD on dialysis	Any	5 mg once after dialysis session
Patients with cGVHD		
Moderate or Severe	Any	5 mg twice daily
ESRD on dialysis	Any	10 mg once after dialysis session

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	Greater than 150 × 109/L	No dose adjustment
Mild, Moderate, or Severe (Child - Pugh Class A, B, C)	100 × 109/L to 150 × 109/L	10 mg twice daily
	50 to less than 100 × 109/L	5 mg daily
	Less than 50 × 109/L	Avoid use
Hepatic Impairment Status	**Platelet Count**	**Recommended Starting Dosage**
Patients with PV Mild, Moderate, or Severe (Child -Pugh Class A, B, C)	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
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 hey occur

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 asogastric 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.

PHARMACOKINETICS

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (Cmax) achieved approximately 1 hour post-dose. Based on a human mass balance study, oral absorption of ruxolitinib, as ruxolitinib or metabolites formed under first-pass, is 95% or greater. Mean ruxolitinib Cmax and total exposure (AUC) increased proportionally over a single dose range of 5-200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean Cmax was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

Distribution

The mean volume of distribution at steady state is approximately 75 liters in MF and PV patients. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins in vitro is approximately 97%, mostly to albumin.

A whole body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

Biotransformation

Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with additional contribution from CYP2C9. Parent compound is the predominant entity in human plasma, representing approximately 60% of the drug-related material in circulation. Two major and active metabolites are present in plasma representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contributes to 18% of the overall pharmacodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on in vitro studies. In vitro data indicate that ruxolitinib may inhibit P-gp and BCRP.

Elimination

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half-life of ruxolitinib is approximately 3 hours. Following a single oral dose of [14C]-labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74% of radioactivity excreted in urine and 22% via faeces. Unchanged parent substance accounted for less than 1% of the excreted total radioactivity.

WARNINGS AND PRECAUTIONS

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.

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

Tuberculosis infection has been reported in patients receiving Ruxolitinib. Observe patients receiving Ruxolitinib for signs and symptoms of active tuberculosis and manage promptly.

Prior to initiating Ruxolitinib, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed

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

Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected.

Hepatitis B

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.

Symptom Exacerbation Following Interruption or Discontinuation of Treatment

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 812 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.

Pregnancy

There are no data from the use of Ruxolitinib in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic.

Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. The potential risk for humans is unknown. As a precautionary measure, the use of Ruxolitinib during

Pregnancy is contraindicated.

Women of childbearing potential/Contraception

Women of child-bearing potential should use effective contraception during the treatment with Ruxolitinib. In case pregnancy should occur during treatment with Ruxolitinib, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus.

Breast-feeding

Ruxolitinib must not be used during breast-feeding and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available

Pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk.

Fertility

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

SIDE EFFECTS

Following are the side effects observed with the use of ruxolitinib:

- 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

DRUG INTERACTIONS

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

Interactions resulting in dose reduction of ruxolitinib

CYP3A4 inhibitors

Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib Cmax and AUC that were higher by 33% and 91%, respectively, than with ruxolitinib alone.

The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

When administering ruxolitinib with strong CYP3A4 inhibitors the unit dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily, except in GvHD patients. The effect of strong CYP3A4 inhibitors in patients with GvHD was not found to have a significant impact on any parameter in the population pharmacokinetic model.

Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy.

Dual CYP2C9 and CYP3A4 inhibitors

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with a dual CYP2C9 and CYP3A4 inhibitor, fluconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 47% and 232%, respectively, than with ruxolitinib alone.

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily.

Enzyme inducers

CYP3A4 inducers (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum).

Patients should be closely monitored and the dose titrated based on safety and efficacy. In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of ruxolitinib alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near Emax. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

Other interactions to be considered affecting ruxolitinib

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine).

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib Cmax and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). However, patients should be closely monitored for cytopenias wh4en initiating therapy with a moderate CYP3A4 inhibitor.

Effects of ruxolitinib on other medicinal products

Substances transported by P-glycoprotein or other transporters

Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised. It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimised if the time between administrations is kept apart as long as possible.

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with ruxolitinib. Another study in healthy subjects indicated that ruxolitinib does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

OVERDOSE

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, anaemia and thrombocytopenia. Appropriate supportive treatment should be given.

Hemodialysis is not expected to enhance the elimination of ruxolitinib.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Pregnancy and lactation.

STORAGE & INSTRUCTIONS

Do not store above 30°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of the children.

Warning: To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED

Mylonib Tablet 5mg
10's, 20's and 60's tablets
Mylonib Tablet 15mg
10's, 20's and 60's tablets
Mylonib Tablet 20mg
10's, 20's and 60's tablets

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

۳۰ ڈگری سینٹی گریڈ درجہ حرارت سے زیادہ پر نہ رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

انتباہ: صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخہ پر فروخت کریں۔

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