

## Dose Adjustment Guideline of Javirux®









### 1. Recommended Dosage for Myelofibrosis

#### 1.1 Treatment Interruption and Restarting Dosing



Interrupt treatment for platelet counts less than  $50 \times 10^9/L$  or absolute neutrophil count (ANC) less than  $0.5 \times 10^9/L$ . After recovery of platelet counts above  $50 \times 10^9/L$  and ANC above  $0.75 \times 10^9/L$ , dosing may be restarted. Table 1 illustrates the maximum allowable dose that may be used in restarting Javirux after a previous interruption.

Table 1: Myelofibrosis: Maximum Restarting Doses for Javirux® after Safety Interruption for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of  $100 \times 10^9/L$  or Greater

 Current Platelet Count	Maximum Dose When Restarting Javirux® Treatment*
Greater than or equal to $125 \times 10^9/L$	20 mg 
100 to less than $125 \times 10^9/L$	15 mg 
75 to less than $100 \times 10^9/L$	10 mg  for at least 2 weeks; if stable, may increase to 15 mg 
50 to less than $75 \times 10^9/L$	5 mg  for at least 2 weeks; if stable, may increase to 10 mg 
Less than $50 \times 10^9/L$	

\*Maximum doses are displayed. When restarting, begin with a dose at least 5 mg twice daily below the dose at interruption.




















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Following treatment interruption for ANC below  $0.5 \times 10^9/L$ , after ANC recovers to  $0.75 \times 10^9/L$  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.

### 1.2 Dose Reductions



Dose reductions should be considered if the platelet counts decrease as outlined in Table 2 with the goal of avoiding dose interruptions for thrombocytopenia.

Table 2: Myelofibrosis: Dosing Recommendations for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of  $100 \times 10^9/L$  or Greater

Platelet Count	Dose at Time of Platelet Decline				
	25 mg  2x daily	20 mg  2x daily	15 mg  2x daily	10 mg  2x daily	5 mg  2x daily
	New Dose	New Dose	New Dose	New Dose	New Dose
100 to less than $125 \times 10^9/L$	20 mg  2x daily	15 mg  2x daily	<b>NO CHANGES</b>	<b>NO CHANGES</b>	<b>NO CHANGES</b>
75 to less than $100 \times 10^9/L$	10 mg  2x daily	10 mg  2x daily	10 mg  2x daily	<b>NO CHANGES</b>	<b>NO CHANGES</b>
50 to less than $75 \times 10^9/L$	5 mg  2x daily	5 mg  2x daily	5 mg  2x daily	5 mg  2x daily	<b>NO CHANGES</b>
Less than $50 \times 10^9/L$	 <b>HOLD</b>	 <b>HOLD</b>	 <b>HOLD</b>	 <b>HOLD</b>	 <b>HOLD</b>


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

If the response is insufficient and platelet and neutrophil counts are adequate, doses may be increased in 5 mg  increments to a maximum of 25 mg . 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:

- 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);
- Platelet count greater than  $125 \times 10^9/L$  at 4 weeks and platelet count never below  $100 \times 10^9/L$ ;
- ANC levels greater than  $0.75 \times 10^9/L$ .

Based on limited clinical data, long-term maintenance at a 5 mg  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 Javirux® if there is no spleen size reduction or symptom improvement after 6 months of therapy.



**ENLARGED SPLEEN**

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### 1.4 Dose Modifications for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with Platelet Counts of $50 \times 10^9/L$ to Less Than $100 \times 10^9/L$

This section applies only to patients with platelet counts of  $50 \times 10^9/L$  to less than  $100 \times 10^9/L$  prior to any treatment with Javirux®.



### 1.5 Treatment Interruption and Restarting Dosing










- Interrupt treatment for platelet counts less than  $25 \times 10^9/L$  or ANC less than  $0.5 \times 10^9/L$ .
- After recovery of platelet counts above  $35 \times 10^9/L$  and ANC above  $0.75 \times 10^9/L$ , 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  $25 \times 10^9/L$  or ANC below  $0.5 \times 10^9/L$  that led to dose interruption.

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### 1.6 Dose Reductions

Reduce the dose of Javirux® for platelet counts less than  $35 \times 10^9/L$  as described in Table 3.

**Table 3: Myelofibrosis: Dosing Modifications for Thrombocytopenia for Patients with Starting Platelet Count of  $50 \times 10^9/L$  to Less Than  $100 \times 10^9/L$**

Platelet Count	Dosing Recommendations
Less than $25 \times 10^9/L$	
$25 \times 10^9/L$ to less than $35 \times 10^9/L$ AND the platelet count decline is less than 20% during the prior four weeks	<ul style="list-style-type: none"> <li>Decrease dose by 5 mg .</li> <li>For patients on 5 mg , maintain dose at 5 mg .</li> </ul>
$25 \times 10^9/L$ to less than $35 \times 10^9/L$ AND the platelet count decline is 20% or greater during the prior four weeks	<ul style="list-style-type: none"> <li>Decrease dose by 5 mg .</li> <li>For patients on 5 mg , decrease the dose to 5 mg .</li> <li>For patients on 5 mg , maintain dose at 5 mg .</li> </ul>

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### **1.7 Dose Modifications Based on Insufficient Response for Patients with Myelofibrosis and Starting Platelet Count of $50 \times 10^9/L$ to Less Than $100 \times 10^9/L$**

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, doses may be increased in 5 mg twice daily increments to a maximum of 10 mg twice daily if all of the following criteria are met:

- a. the platelet count has remained at least  $40 \times 10^9/L$ ,
- b. the platelet count has not fallen by more than 20% in the prior 4 weeks, and
- c. the ANC is more than  $1 \times 10^9/L$ , 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 Javirux® if there is no spleen size reduction or symptom improvement after 6 months of therapy.

### **1.8 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 Javirux® at a lower dose.



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### 2. Recommended Dosage for Polycythemia Vera

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

#### 2.1 Dose Reductions

Dose reductions should be considered for hemoglobin and platelet count decreases as described in Table 4.

Table 4: Polycythemia Vera: Dose Reductions

Hemoglobin and/or Platelet Count	Dosing Recommendations
Hemoglobin greater than or equal to 12 g/dL <b>AND</b> platelet count greater than or equal to $100 \times 10^9/L$	
Hemoglobin 10 to less than 12 g/dL <b>AND</b> platelet count 75 to less than $100 \times 10^9/L$	<ul style="list-style-type: none"> <li>Dose reductions should be considered with the goal of avoiding dose interruptions for anemia and thrombocytopenia.</li> </ul>
Hemoglobin 8 to less than 10 g/dL <b>OR</b> platelet count 50 to less than $75 \times 10^9/L$	<ul style="list-style-type: none"> <li>Reduce dose by 5 mg  .</li> <li>For patients on 5 mg  , decrease the dose to 5 mg  .</li> </ul>
Hemoglobin less than 8 g/dL <b>OR</b> platelet count less than $50 \times 10^9/L$	






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### 2.2 Treatment Interruption and Restarting Dosing

- Interrupt treatment for hemoglobin less than 8 g/dL, platelet counts less than  $50 \times 10^9/L$  or ANC less than  $1.0 \times 10^9/L$ .
- After recovery of the hematologic parameter(s) to acceptable levels, dosing may be restarted.
- Table 5 illustrates the dose that may be used in restarting Javirux® after a previous interruption.



**Table 5: Polycythemia Vera: Restarting Doses for Javirux® 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 $50 \times 10^9/L$ OR ANC less than $1 \times 10^9/L$	
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than $75 \times 10^9/L$ OR ANC 1 to less than $1.5 \times 10^9/L$	5 mg  or no more than 5 mg  less than the dose which resulted in dose interruption
Hemoglobin 10 to less than 12 g/dL OR platelet count 75 to less than $100 \times 10^9/L$ OR ANC 1.5 to less than $2 \times 10^9/L$	10 mg  or no more than 5 mg  less than the dose which resulted in dose interruption



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Hemoglobin greater than or equal to 12 g/dL OR platelet count greater than or equal to $100 \times 10^9/L$ OR ANC greater than or equal to $2 \times 10^9/L$	15 mg  * or no more than 5 mg  less than the dose which resulted in dose interruption
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\* Continue treatment for at least 2 weeks; if stable, may increase dose by 5 mg twice daily.



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

### 2.3 Dose Management after Restarting Treatment

After restarting Javirux® 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 Javirux® would not be limited.

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### 2.4 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  increments to a maximum of 25 mg . 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. 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  $140 \times 10^9/L$
3. Hemoglobin greater than or equal to 12 g/dL
4. ANC greater than or equal to  $1.5 \times 10^9/L$

### 3. Recommended Dosage for Acute Graft-Versus-Host Disease

- The recommended starting dose of Javirux® is 5 mg given orally . Consider increasing the dose to 10 mg  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 Javirux®.
- Consider tapering Javirux® after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper Javirux® by one dose level approximately every 8 weeks (10 mg  to 5 mg  to 5 mg ). If aGVHD signs or symptoms recur during or after the taper of Javirux®, consider retreatment.

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- 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 Javirux® for adverse reactions as described in Table 6. For dose reductions, patients who are currently receiving Javirux® 10 mg  may have their dose reduced to 5 mg ; patients receiving 5 mg  may have their dose reduced to 5 mg . Patients who are unable to tolerate Javirux® at a dose of 5 mg  should have treatment interrupted until their clinical and/or laboratory parameters recover.

**Table 6: 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 $1 \times 10^9/L$ considered related to Javirux®	Hold Javirux® for up to 14 days; resume at 1 dose level lower upon recovery.
Total Bilirubin elevation, no liver GVHD	$3.0-5.0 \times ULN$ : Continue Javirux® at 1 dose level lower until recovery. $> 5.0-10.0 \times ULN$ : Hold Javirux® for up to 14 days until bilirubin $\leq 1.5 \times ULN$ ; resume at current dose upon recovery. Total bilirubin $> 10.0 \times ULN$ : Hold Javirux® for up to 14 days until bilirubin $\leq 1.5 \times ULN$ ; resume at 1 dose level lower upon recovery.
Total Bilirubin elevation, liver GVHD	$> 3.0 \times ULN$ : Continue Javirux® at 1 dose level lower until recovery.

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### 4. Recommended Dosage for Chronic Graft-Versus-Host Disease











- The recommended starting dose of Javirux® is 10 mg given orally  2x daily.
- Consider tapering Javirux® after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper Javirux® by one dose level approximately every 8 weeks (10 mg  2x daily to 5 mg  2x daily to 5 mg  1x daily). If cGVHD signs or symptoms recur during or after the taper of Javirux®, consider retreatment.
- 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 Javirux® for adverse reactions as described in Table 7. For dose reductions, patients who are currently receiving Javirux® 10 mg  2x daily may have their dose reduced to 5 mg  2x daily; patients receiving 5 mg  2x daily may have their dose reduced to 5 mg  1x daily. Patients who are unable to tolerate Javirux® at a dose of 5 mg  1x daily should have treatment interrupted until their clinical and/or laboratory parameters recover.

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

Parameter	Dosing Recommendations
Platelet count less than $20 \times 10^9/L$	Reduce Javirux® 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 $0.75 \times 10^9/L$ considered related to Javirux®	Reduce Javirux® by 1 dose level; resume at initial dose level upon recovery.

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ANC less than $0.5 \times 10^9/L$ considered related to Javirux®	Hold Javirux® for up to 14 days; resume at 1 dose level lower upon recovery. May resume initial dose level when ANC greater than $1.0 \times 10^9/L$ .
Total Bilirubin: $3.0-5.0 \times ULN$	Continue Javirux® 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: $> 5.0-10.0 \times ULN$	Hold Javirux® 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: $> 10.0 \times ULN$	Hold Javirux® 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 Javirux® at 1 dose level lower until recovery.
Other Adverse Reactions: Grade 4	








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### 5. Dose Modifications for Renal or Hepatic Impairment

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





Modify the Javirux® 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 8.

Table 8: Dose Modifications for Renal Impairment

Renal Impairment Status	Platelet Count	Recommended Starting Dosage
<b>Patients with MF</b>		
Moderate or Severe	Greater than $150 \times 10^9/L$	No dose adjustment
	100 to $150 \times 10^9/L$	10 mg  2x daily
	50 to less than $100 \times 10^9/L$	5 mg  1x daily
	Less than $50 \times 10^9/L$	
ESRD on dialysis	100 to $200 \times 10^9/L$	15 mg  after dialysis session 1x daily
	Greater than $200 \times 10^9/L$	20 mg  after dialysis session 1x daily
<b>Patients with PV</b>		
Moderate or Severe	Any	5 mg  2x daily
ESRD on dialysis	Any	10 mg  after dialysis session 1x daily



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Renal Impairment Status	Platelet Count	Recommended Starting Dosage
<b>Patients with aGVHD</b>		
Moderate or Severe	Any	5 mg  1x daily
ESRD on dialysis	Any	5 mg  1x daily after dialysis session
<b>Patients with cGVHD</b>		
Moderate or Severe	Any	5 mg  2x daily
ESRD on dialysis	Any	10 mg  1x daily after dialysis session

ESRD = end stage renal disease and CLcr = creatinine clearance


### 5.2 Hepatic Impairment

Modify the Javirux® dosage for patients with hepatic impairment according to Table 9.

Table 9: 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 <sup>9</sup> /L	No dose adjustment
	100 to less than 150 × 10 <sup>9</sup> /L	10 mg  2x daily
	50 to less than 100 × 10 <sup>9</sup> /L	5 mg  1x daily
	Less than 50 × 10 <sup>9</sup> /L	Avoid use

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Hepatic Impairment Status	Platelet Count	Recommended Starting Dosage
Patients with PV Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Any	5 mg  2x daily
Patients with aGVHD Mild, Moderate, or Severe based on NCI criteria without liver GVHD	Any	No dose adjustment
Stage 1 or 2 Liver aGVHD	Any	No dose adjustment
Stage 4 Liver aGVHD	Any	5 mg  1x 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 Javirux® dosage for hematologic toxicities and liver impairment.