Indications and Usage
Jakafi 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.

Important safety considerations
- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. 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.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

Please see Important Safety Information on the last page for related and other risk information. Please click here for Full Prescribing Information for complete dosing recommendations.
Early dose adjustments as needed to optimize efficacy and safety

In the phase 2 COMFORT I trial, 60% of patients treated with Jakafi and 30% of patients receiving placebo achieved a ≥35% reduction in spleen volume from baseline to week 12. In COMFORT-II, 60% of patients treated with Jakafi and 38% of patients receiving placebo in the COMFORT II study with 309 patients with intermediate-2–risk or high-risk myelofibrosis. The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI.

In COMFORT-I, 60% of patients treated with Jakafi and 30% of patients receiving placebo achieved a ≥35% reduction in spleen volume from baseline to week 12. COMFORT-II was a randomized, double-blind, placebo-controlled phase 3 study with 219 patients with intermediate-2–risk or high-risk myelofibrosis. The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI.

Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy. Continued use of therapy for more than 6 months should be limited to patients in whom the benefits outweigh the risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

If patient meets all these criteria:
- Stabilized and then as clinically indicated.
- Insufficient spleen reduction
- In the case of an insufficient response, consider an increase in the dose if patient meets all of the above.
- Insufficient spleen reduction
- Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy. Continued use of therapy for more than 6 months should be limited to patients in whom the benefits outweigh the risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

Thrombocytopenia

Monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. The recommended starting dose of Jakafi for MF is based on PLT count.

PLT Count

50 to <100

10 to 15 mg
twice daily

15 to 20 mg
twice daily

20 to 25 mg
twice daily

25 to >30 mg
twice daily

30 to >50 mg
twice daily

50 to >100

5 mg twice daily

10 mg twice daily

20 mg twice daily

30 mg twice daily

5 mg once daily

10 mg once daily

20 mg once daily

30 mg once daily

The recommended starting dose in MF for patients with a starting PLT count of 50 to <100 × 10^11/L is 5 mg twice daily.

Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks if patient meets all these criteria:

Insufficient spleen reduction

PLT count has remained <40 × 10^11/L and has not decreased by >20% in the prior 4 weeks

Adequate spleen reduction

No dose reduction or interruption for an adverse event or hematological toxicity in the prior 4 weeks

Continue treatment of for more than 6 months should be limited to patients in whom the benefits outweigh the risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

If patient meets all these criteria:
- Stabilized and then as clinically indicated.
- Insufficient spleen reduction
- In the case of an insufficient response, consider an increase in the dose if patient meets all of the above.
- Insufficient spleen reduction
- Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy. Continued use of therapy for more than 6 months should be limited to patients in whom the benefits outweigh the risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

Thrombocytopenia

Monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

PLT count has remained ≥40 × 10^11/L in the prior 4 weeks

If patient meets all these criteria:
- Stabilized and then as clinically indicated.
- Insufficient spleen reduction
- In the case of an insufficient response, consider an increase in the dose if patient meets all of the above.
- Insufficient spleen reduction
- Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy. Continued use of therapy for more than 6 months should be limited to patients in whom the benefits outweigh the risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

Insufficient spleen reduction

PLT count has remained <40 × 10^11/L and has not decreased by >20% in the prior 4 weeks

Adequate spleen reduction

No dose reduction or interruption for an adverse event or hematological toxicity in the prior 4 weeks

Continue treatment of for more than 6 months should be limited to patients in whom the benefits outweigh the risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

If patient meets all these criteria:
- Stabilized and then as clinically indicated.
- Insufficient spleen reduction
- In the case of an insufficient response, consider an increase in the dose if patient meets all of the above.
- Insufficient spleen reduction
- Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy. Continued use of therapy for more than 6 months should be limited to patients in whom the benefits outweigh the risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.
START here

A CBC and platelet (PLT) count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized and then as clinically indicated. The recommended starting dose of Jakafi for MFS is based on PLT count.

<table>
<thead>
<tr>
<th>PLT Count (× 10^9/L)</th>
<th>Recommended Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>50 to 200</td>
<td>15 mg twice daily</td>
</tr>
<tr>
<td>&gt;200</td>
<td>20 mg twice daily</td>
</tr>
</tbody>
</table>

Jakafi is also available in 10 mg and 25 mg tablets.

**Early dose adjustments as needed to optimize safety and efficacy**

In the phase 2 COMFORT trial of patients with intermediate-2- or high-risk MFS, the primary endpoint was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to 24 weeks. Of patients receiving placebo (P = 0.0005).

**Optimize** to balance safety and efficacy

**INCREASE DOSE**

In the case of an insufficient response, consider an increase in the dose if patient meets all criteria below.

- Insufficient spleen reduction
- PLT count >25 mg/L at 4 weeks and mean >100 × 10^9/L
- Absolute neutrophil count (ANC) >7.5 × 10^9/L

Increase dose by 5-mg twice-daily increments to a maximum of 25 mg twice daily.

Doses should not increase during the first 4 weeks of therapy and not more frequently than every 2 weeks.

**DECREASE DOSE**

In the case of a HemaToxilin Toxicity including:

- Thrombocytopenia
- Discontinue Jakafi in patients with a starting platelet count of 50 to <100 × 10^9/L.

**MONITOR** frequently

In patients receiving Jakafi in the COMFORT studies, PLT counts and hemoglobin levels generally stabilized after 8 to 12 weeks.

- <1% of patients receiving Jakafi in the COMFORT studies discontinued due to anemia or thrombocytopenia.

**Interrupt Jakafi treatment for:**

- Bleeding requiring intervention, regardless of current platelet count.
- Thrombocytopenia (PLT <50 × 10^9/L), or
- Neutropenia (ANC <0.5 × 10^9/L).

See RESTARTING tab for dose modifications.

**Risk for thrombocytopenia, anemia, and neutropenia**

- Treatment with Jakafi can cause thrombocytopenia, anemia, and neutropenia, which are each dose-related effects.
- Patients may require dose reductions to maintain PLT count >125 × 10^9/L and ANC >0.75 × 10^9/L. Consider increasing the dose if the underlying cause of bleeding has been controlled. If the bleeding event resolved, please refer to the tying the incidence of anemia, and neutropenia in patients receiving Jakafi.

**Current PLT Count (× 10^9/L)**

- Maximum restarting doses for Jakafi after safety interruption for thrombocytopenia

- Following treatment interruption for ANC <0.5 × 10^9/L, after ANC recovers to ≥0.75 × 10^9/L, restart dosing at the highest of 5 mg once daily or 5 mg twice daily below the largest dose in the prior week.

**Restarting in case of bleeding**

- 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 Jakafi at a lower dose.

Please see Important Safety Information on the last page for related and other risk information.

**Please click here for Full Prescribing Information for complete dosing recommendations.**

**In COMFORT-I, phase 3 treatment with Jakafi required a mean change in spleen volume at week 24 vs 0.7% of patients receiving placebo (P = 0.0005).**

**In COMFORT-I, grade 3 and 4 thrombocytopenia or anemia occurred in 30% and 6% of patients receiving Jakafi, respectively.**

**In COMFORT-I, grade 3 and 4 neutropenia occurred in 20% and 3% of patients receiving Jakafi, respectively.**

**Maximum restarting doses for Jakafi after safety interruption for thrombocytopenia**

**Current PLT Count (× 10^9/L)**

- >125
- 20 mg twice daily
- 100 to <125
- 15 mg twice daily
- 75 to <100
- 10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
- 50 to <75
- 5 mg twice daily for at least 2 weeks; if stable, may increase to 10 mg twice daily
- <50
- Continuous hold

Modern trials completed with Jakafi (Ruxolitinib) in 10 mg and 25 mg tablets.

See STARTING PLT COUNT TO <100 × 10^9/L for recommended dose modifications in patients with a starting platelet count of 50 to <100 × 10^9/L.

**Please see Important Safety Information on the last page for related and other risk information.**

**Please click here for Full Prescribing Information for complete dosing recommendations.**

**In COMFORT-I, 1,2, and 3 weeks after initiating therapy, patients were assessed for a ≥35% reduction in spleen volume from baseline to endpoint.**

**In COMFORT-I, 3 weeks after initiating therapy, the proportion of patients achieving an intermediate-2–risk or high-risk MF, the primary endpoint, was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to 24 weeks.**

**In COMFORT-Ia: Mean Change in Spleen Volume by Dose at Week 24**

<table>
<thead>
<tr>
<th>PLT Count (× 10^9/L)</th>
<th>Mean Change in Spleen Volume (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100</td>
<td>−16.7 (−28.1 to −40.2)</td>
</tr>
<tr>
<td>50 to &lt;100</td>
<td>−23.1 (−36.3 to −30.4)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>−36.3 (−39.5 to −33.4)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>−40.5 (−42.3 to −38.5)</td>
</tr>
</tbody>
</table>

**In COMFORT-I, phase 3 treatment with Jakafi required a mean change in spleen volume at week 24 vs 0.7% of patients receiving placebo (P = 0.0005).**
INCREASE DOSE

In the case of an insufficient response, consider an increase in the dose if patient meets all of these criteria:

- Insufficient spleen reduction
- PLT count: >25 × 10^9/L
- Absolute neutrophil count (ANC) >0.5 × 10^9/L

Increase dose by 5-mg twice-daily increments to a maximum of 25 mg twice daily

Decrease dose by 5-mg twice-daily increments to a maximum of 25 mg twice daily

In the case of an insufficient response, temporary withholding Jakafi for 7 to 14 days while closely monitoring PLT counts may be necessary, then re-initiate Jakafi at a reduced dose.

DECREASE DOSE

In the case of a hematologic toxicity including:

- Thrombocytopenia

Discontinuation can be avoided by reducing the dose or temporarily withholding Jakafi

In patients receiving Jakafi in the COMFORT studies, mean decreases in hemoglobin reached a nadir of approximately 1.3 to 2.0 g/dL before baseline after 12 weeks of therapy and then gradually recovered to near steady state that was approximately 0.5 g/dL below baseline.

Omit or initiate thalidomide or lenalidomide doses of >200 mg daily with Jakafi

In patients receiving Jakafi and/or blood transfusions may be required for patients developing anemia

In COMFORT-I, 30% of patients treated with Jakafi and 20% of patients receiving placebo received red blood cell transfusions before a response, which are dose-related effects. Patients receiving a starting PLT count of ≥10 mg twice daily should be limited to patients in whom the benefits outweigh the potential risks.

Anemia

Dose modifications of Jakafi and/or blood transfusions may be required for patients developing anemia

In COMFORT-I, 40% of patients treated with Jakafi and 30% of patients receiving placebo received red blood cell transfusions before a response, which are dose-related effects. Patients receiving a starting PLT count of ≥10 mg twice daily should be limited to patients in whom the benefits outweigh the potential risks.

MONITOR frequently

In patients receiving Jakafi in the COMFORT studies, PLT counts and hemoglobin levels generally stabilized after 1 to 2 months.

In COMFORT-I, grade 3 and 4 thrombocytopenia or anemia occurred in 15% and 16% of patients receiving Jakafi, respectively.

In patients receiving Jakafi in the COMFORT studies dose discontinuation due to anemia or thrombocytopenia was observed.

INTEGRATED THERAPY

Jakafi® treatment can cause thrombocytopenia, anemia, and neutropenia, which are each dose-related effects. Patients receiving Jakafi with a PLT count:

- ≥10 mg twice daily

Monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

OUTBREAK DOSE

Interrupt Jakafi treatment for:

- Bleeding requiring interventions, regardless of current platelet count,
- Thrombocytopenia (PLT ≤10 × 10^9/L), or
- Neutropenia (ANC ≤0.5 × 10^9/L)

See RESTARTING tab for dose modifications.

RISK FOR THROMBOCYTOPENIA, ANEMIA, AND NEUTROPENIA

Treatment with Jakafi can cause thrombocytopenia, anemia, and neutropenia, which are each dose-related effects. Patients receiving Jakafi with a PLT count:

- ≥10 mg twice daily

Monitor PLT, platelet.

Avoid the use of CYP3A4 inhibitors and fluconazole doses of >200 mg daily with Jakafi

Additional dose modifications should be made with careful monitoring of safety and efficacy

Drug interactions

Modify the dose of Jakafi® (ruxolitinib) when coadministered with strong CYP3A4 inhibitors and fluconazole doses of >200 mg daily:

- Avoid the use of CYP3A4 inhibitors of >200 mg daily with Jakafi
- Additional dose modifications should be made with careful monitoring of safety and efficacy

Special Populations

For Patients Coadministered Strong CYP3A4 Inhibitors or Fluconazole Doses of >200 mg

Starting dose for patients with MF with a PLT count:

- >100 × 10^9/L: 10 mg twice daily
- 100 × 10^9/L – 10 × 10^9/L: 5 mg twice daily
- <10 × 10^9/L: 5 mg once daily

If on stable dose for patients with MF:

- >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: 5 mg once daily

Avoid strong CYP3A4 inhibitor or fluconazole treatment, or interrupt treatment with Jakafi for the duration of strong CYP3A4 inhibitor or fluconazole use

For suggested starting dose recommendations.

Please see Important Safety Information on the back cover for related and other risk information. Please click here for Full Prescribing Information for complete prescribing recommendations.

Please see Important Safety Information on the last page for related and other risk information.
Important Safety Information

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. 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
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5 \( \times 10^9 \)/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- In myelofibrosis and polycythemia vera, the three most common nonhematologic adverse reactions (incidence >10%) were bruising, dizziness and headache. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections and edema
- Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for two weeks after the final dose

Please click here for Full Prescribing Information for Jakafi.

References: