Jakafi® (ruxolitinib) Efficacy and Safety Data in Patients With Intermediate-1–Risk MF

Ruxolitinib (Jakafi) is a Category 2A* treatment option for both symptomatic lower-risk† and higher-risk MF – in patients with platelets ≥50 x 10⁹/L.‡

*Category 2A: Based upon lower-level evidence compared to Category 1; there is uniform NCCN consensus that the intervention is appropriate.‡
† Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM, low or intermediate risk on MIPSS-70 (threshold of ≤3 prognostic variable points), and very low, low, or intermediate risk based on MIPSS-70+ (version 2.0; threshold of ≤3 prognostic variable points).‡
‡ In patients who are not transplant candidates.

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. 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. In patients with cytopenias, consider dose reductions or temporarily withholding Jakafi or transfusions, as clinically indicated.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Evaluate patients prior to and while receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

Please see related and other Important Safety Information on the last page. Please click here to see Full Prescribing Information for Jakafi.
Myelofibrosis (MF) is a serious disease that may require active management at diagnosis.

In MF, the presence of any one of the following risk factors* indicates that a patient is already intermediate risk:

- Hemoglobin level <10 g/dL
- Leukocyte count >25 × 10^9/L
- Age >65 years
- Red cell transfusion dependency
- Circulating blast cells ≥1%
- Platelet count <100 × 10^9/L
- Constitutional symptoms
- Unfavorable karyotype

In a post hoc, pooled analysis of overall survival in the COMFORT studies (N = 528), there was a 14% increase in the risk of death for each additional 5 dL in spleen volume at baseline over 3 years (HR, 1.14; 95% CI, 1.07-1.21).7† These increases were seen irrespective of treatment.7

Myelofibrosis (MF) is a serious disease that may require active management at diagnosis.

In a study of 1054 patients with primary MF, approximately 90% of patients for whom data were available had palpable splenomegaly at diagnosis.5

Larger baseline spleen volume was associated with incremental increases in the risk of death.7

A palpable spleen of ≥5 cm below the left costal margin constitutes progressive disease,* according to the IWG-MRT and ELN response criteria.4

In a post hoc pooled analysis of overall survival with ruxolitinib was performed using data from the two phase 3 studies: COMFORT-I, a randomized, double-blind, placebo-controlled study with 309 patients with intermediate-2–risk or high-risk MF, and COMFORT-II, a randomized, open-label study with 219 patients with intermediate-2–risk or high-risk MF. In COMFORT-I and COMFORT-II, the primary endpoint in both studies was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.6

Imaging, including ultrasound, may be appropriate for patients with a body habitus which precludes palpation.8

* As included in the Dynamic International Prognostic Scoring System Plus tool.

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

- 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 × 10^9/L) was generally reversible by withholding Jakafi until recovery.

When do you intervene in patients with intermediate- or high-risk MF?

New or increasing splenomegaly is considered to be a marker of disease progression.6

In a study of 1054 patients with primary MF, approximately 90% of patients for whom data were available had palpable splenomegaly at diagnosis.5

Data were available for 788 patients, 681 of whom had palpable splenomegaly.6

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**COMFORT-I Primary Endpoint**

42% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 24 vs 0.7% of patients receiving placebo (P < 0.0001).

4.4 years median duration of spleen response among primary responders (n = 65).

**COMFORT-I Percentage Change in Spleen Volume in Individual Patients From Baseline to Week 24 or Last Observation**

Each bar represents an individual patient’s response.


**COMFORT-II Primary Endpoint**

29% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 48 vs 0% of patients receiving best available therapy (P < 0.0001).

**Jakafi adverse reactions**

**COMFORT-I hematologic adverse reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (n = 155)</th>
<th>Placebo (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>96</td>
<td>45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>7</td>
</tr>
</tbody>
</table>

**COMFORT-I nonhematologic adverse reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (n = 155)</th>
<th>Placebo (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruising</td>
<td>23</td>
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<tr>
<td>Dizziness</td>
<td>18</td>
<td>&lt;1</td>
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<tr>
<td>Headache</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>2</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

**Additional Nonhematologic Abnormalities**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (n = 155)</th>
<th>Placebo (n = 151)</th>
</tr>
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<tbody>
<tr>
<td>ALT</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>AST</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Cholesterol elevation</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

Please see related and other Important Safety Information on the last page. Please click here to see Full Prescribing Information for Jakafi.
Jakafi® (ruxolitinib) safety and tolerability data: JUMP expanded-access study

JUMP study design

- JUMP (JAK Inhibitor RUXolitinib in Myelofibrosis Patients) was a single-arm, open-label, phase 3b, expanded-access study that enrolled adult patients with primary or secondary MF classified as intermediate-1–, intermediate-2–, or high-risk MF. Patients with intermediate-1–risk MF were required to have a palpable spleen (≥5cm from the costal margin).
- The study enrolled 2233 patients. At study entry, 835 patients had intermediate-1–risk MF, 755 patients had intermediate-2–risk MF, and 194 patients had high-risk MF.
- The primary endpoint was assessment of Jakafi safety and tolerability by the frequency, duration, and severity of adverse events. Additional endpoints included the proportion of patients with ≥50% reduction in palpable spleen length.

JUMP hematologic adverse events

<table>
<thead>
<tr>
<th>Hematologic adverse events (% of patients)</th>
<th>Full cohort (N = 2233)</th>
<th>Intermediate-1–risk MF (N = 835)</th>
<th>Intermediate-2– and high-risk MF (N = 949)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades, %</td>
<td>Grade 3 and 4, %</td>
<td>All Grades, %</td>
</tr>
<tr>
<td>Anemia</td>
<td>60</td>
<td>35</td>
<td>57</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
<td>19</td>
<td>43</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>5</td>
<td>6</td>
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<tr>
<td>Diarrhea</td>
<td>13</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15</td>
<td>2</td>
<td>16</td>
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<tr>
<td>Peripheral edema</td>
<td>9</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>0</td>
<td>12</td>
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<tr>
<td>Dyspnea</td>
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<td>2</td>
<td>8</td>
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<tr>
<td>Abdominal pain</td>
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<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>7</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
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<td>Dizziness</td>
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In the overall JUMP population, the safety profile was generally consistent with previous reports for Jakafi

- 58% of all enrolled patients (n = 1283) completed treatment per protocol.
- Complete treatment was defined as undergoing treatment for up to 24 months after the last patient’s first visit or transitioning to a commercial drug.
- The most common adverse events leading to discontinuation were thrombocytopenia (3%, 58/1784) and anemia (2%, 35/1784).

JUMP efficacy data: Reduction in spleen length by disease severity

- At week 96, 67% (423/636) of efficacy evaluable patients achieved a ≥50% reduction from baseline in palpable spleen length.

Intermediate-1–risk MF and intermediate-2–risk MF to high-risk MF

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- 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 × 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 intermittent 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 most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. 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 2 weeks after the final dose.

Please click here to see Full Prescribing Information for Jakafi.