Understanding how Jakafi® (ruxolitinib) inhibits* overactive JAK pathway signaling

*Jakafi, a kinase inhibitor, inhibits JAK1 and JAK2 (Janus-associated kinases 1 and 2), which mediate the signaling of cytokines and growth factors important for hematopoiesis and immune function.1

Indications and Usage
Jakafi is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

Please see Important Safety Information on the back cover and accompanying Full Prescribing Information.
Polycythemia vera

Polycythemia vera (PV) is a chronic, progressive myeloproliferative neoplasm (MPN) characterized by increased myeloid, erythroid, and megakaryocytic cell proliferation without significant bone marrow fibrosis.1,2,3 Erythrocytosis (elevated total red blood cell mass) is the most prominent clinical expression of PV, and it distinguishes PV from all other MPNs, including essential thrombocythemia and primary myelofibrosis (MF).4

PV may progress to MF as bone marrow becomes more fibrotic.5

Myelofibrosis

MF is a serious, progressive hematologic malignancy characterized by bone marrow fibrosis, abnormal cytokine expression, extramedullary hematopoiesis, constitutional symptoms, anemia, and shortened survival.6 All of the signs or symptoms are not necessarily present in all patients.6 Extramedullary hematopoiesis often results in splenomegaly.7 Newly detected or recent growth of a palpable spleen is a sign of disease progression.8

Median overall survival in intermediate-2–risk or high-risk MF is less than 5 years.9

References:
Overactive JAK pathway signaling is a key mechanism of disease\textsuperscript{14,15}

Factors that impact JAK signaling\textsuperscript{16-24}
- JAK2 mutations
- MPL mutations
- Excess cytokines
- Increased JAK1 signaling
- Impaired negative signaling mechanisms (eg, those involving SOCS)

JAK, Janus-associated kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia virus oncogene; PV, polycythemia vera; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription.
The importance of the JAK pathway

1. Signaling of the JAK pathway plays a key role in normal cell functioning

2. JAK-STAT signaling activates transcription in the nucleus

JAK, Janus-associated kinase; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling.
Well-regulated JAK signaling is essential for cell production, cell proliferation, and immune function. Intracellular regulators, such as suppressor of cytokine signaling (SOCS), help regulate JAK signaling.

Cytokines bind to receptors and activate JAKs. JAKs activate signal transducers and activators of transcription (STATs), which dimerize and enter the nucleus. Inside the nucleus the STATs bind to DNA, stimulating the expression of genes related to cell survival, differentiation, and proliferation.

The JAK-STAT pathway may become overactive by a number of mechanisms. Somatic mutations primarily involve JAK2, calreticulin (CALR), or myeloproliferative leukemia virus oncogene (MPL); approximately 90% of patients with MF carry one of these mutations. Approximately 95% of patients with PV have the JAK2V617F mutation. Other mechanisms noted may be increased JAK1 signaling, an excess of cytokines activating the receptors, or impaired intracellular regulators such as SOCS.
Jakafi® (ruxolitinib) is an oral JAK1 and JAK2 inhibitor

- Jakafi inhibits JAK pathway signaling. Because it binds in the JAK2 kinase domain, not at the site of the JAK2V617F mutation within the pseudokinase domain, it inhibits both mutant and wild-type JAK2.

- Clinical studies with Jakafi included patients who were JAK2V617F positive or negative.

**Jakafi: Mechanism of action**

[Diagram showing the mechanism of Jakafi inhibiting JAK pathway signaling]

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

- 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.

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

Please see related and other Important Safety Information on back cover and accompanying Full Prescribing Information.
When patients with polycythemia vera demonstrate an inadequate response to or are intolerant of hydroxyurea, consider Jakafi

Approval in PV was based on evidence from the RESPONSE (Randomized study of Efficacy and Safety in POlycythemia vera with JAK iNhibitor ruxolitinib verSus bEst available care) trial, a randomized, open-label, active-controlled phase 3 trial comparing Jakafi with best available therapy in 222 patients with PV who had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy, and exhibited splenomegaly.\(^1\)

**Primary end point**

- A significantly larger proportion of patients in the group receiving Jakafi achieved the primary end point—a composite of hematocrit control and a ≥35% reduction in spleen volume at week 32—compared with best available therapy\(^1\) (23% vs <1%, \(P < 0.0001\))
  - 60% of patients receiving Jakafi and 19% of patients receiving best available therapy achieved hematocrit control
  - 40% of patients receiving Jakafi and <1% of patients receiving best available therapy achieved a ≥35% reduction in spleen volume

**Week-80 results\(^1\)**

- 19 of 25 (76%) patients in the Jakafi arm who achieved a primary response at week 32 maintained their response
- 51 of 66 (77%) patients in the Jakafi arm who achieved hematocrit control at week 32 maintained their response
- 43 of 44 (98%) of patients in the Jakafi arm who had a reduction in spleen volume at week 32 maintained their response

*The composite primary end point was defined as hematocrit control without phlebotomy eligibility and a ≥35% spleen volume reduction as measured by CT or MRI. To achieve the hematocrit control end point, patients could not become eligible for phlebotomy between weeks 8 and 32. Phlebotomy eligibility was defined as hematocrit >45% that is ≥3 percentage points higher than baseline or hematocrit >48% (lower value).\(^1\)

**In patients with intermediate-2–risk or high-risk myelofibrosis**

- In COMFORT-I,\(^1\) 42% of patients taking Jakafi achieved the primary end point, a ≥35% reduction in spleen volume at week 24, compared with 0.7% of patients receiving placebo (\(P < 0.0001\)).\(^{35}\)
- In COMFORT-II,\(^1\) 29% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 48, compared with 0% of patients receiving best available therapy\(^1\) (\(P < 0.0001\)).\(^{36}\)
- Jakafi Prescribing Information includes Kaplan-Meier overall survival curves from COMFORT-I and COMFORT-II

\(^1\) COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 total patients with intermediate-2–risk or high-risk myelofibrosis. The primary end point was the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI.\(^{35}\)

\(^1\) COMFORT-II (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label 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 at week 48 as measured by CT or MRI.\(^{36}\)

\(^1\) Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thio Guanine, danazol, peginterferon alfa-2a, interferon-\(\alpha\), melphalan, acetylsalicylic acid, cytarabine, and colchicine.\(^{36}\)
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 × 10⁹/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
- 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
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended 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 see accompanying Full Prescribing Information for Jakafi.

Jakafi.com/HCP