2.4 Chronic Graft-Versus-Host Disease

The recommended starting dose of Jakafi is 10 mg given orally twice daily.

Consider tapering Jakafi after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper Jakafi 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 Jakafi, 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 Jakafi for adverse reactions as described in Table 8. For dose reductions, patients who are currently receiving Jakafi 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 Jakafi 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 20×10^9/L	Reduce Jakafi 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 0.75×10^9/L considered related to Jakafi	Reduce Jakafi by 1 dose level; resume at initial dose level upon recovery.
ANC less than 0.5×10^9/L considered related to Jakafi	Hold Jakafi for up to 14 days; resume at 1 dose level lower upon recovery. May resume initial dose level when ANC greater than 1.0×10^9/L.
Total Bilirubin: 3.0-5.0 × ULN	Continue Jakafi 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 × ULN	Hold Jakafi 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 × ULN	Hold Jakafi 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 Jakafi at 1 dose level lower until recovery.
Other Adverse Reactions: Grade 4	Discontinue Jakafi.

2.5 Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

Modify the Jakafi dosage when coadministered with strong CYP3A4 inhibitors or doses of less than or equal to 200 mg of fluconazole *[see Drug Interactions (7)]*, according to Table 9. Avoid concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily.

Table 9: Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

For patients coadministered strong CYP3A4 inhibitors or doses of less than or equal to 200 mg of fluconazole	**Recommended Jakafi Dose Modification**
Starting dose for patients with MF with a platelet count:	
• Greater than or equal to 100×10^9/L	10 mg twice daily
• 50×10^9/L to less than 100×10^9/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 Jakafi 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 Jakafi dosage for adverse reactions if they occur *[see Dosage and Administration (2.3, 2.4)]*.

2.6 Dose Modifications for Renal or Hepatic Impairment

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

Modify the Jakafi 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 Jakafi in patients with ESRD (CLcr less than 15 mL/min) not requiring dialysis *[see Use in Specific Populations (8.5)]*.

Table 10: Dose Modifications for Renal Impairment

Renal Impairment Status	Platelet Count	Recommended Starting Dosage
Patients with MF		
Moderate or Severe	Greater than 150 × 10^9/L	No dose adjustment
	100 to 150 × 10^9/L	10 mg twice daily
	50 to less than 100 × 10^9/L	5 mg daily
	Less than 50 × 10^9/L	Avoid use *[see Use in Specific Populations (8.5)]*
ESRD on dialysis	100 to 200 × 10^9/L	15 mg once after dialysis session
	Greater than 200 × 10^9/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

ESRD = end stage renal disease and CLcr = creatinine clearance

Hepatic Impairment

Modify the Jakafi 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 Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Greater than 150 × 10^9/L	No dose adjustment
	100 × 10^9/L to 150 × 10^9/L	10 mg twice daily
	50 to less than 100 × 10^9/L	5 mg daily
	Less than 50 × 10^9/L	Avoid use *[see Use in Specific Populations (8.6)]*

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 Jakafi dosage for adverse reactions if they occur *[see Dosage and Administration (2.3, 2.4)]*.

2.7 Method of Administration

Jakafi 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 Jakafi therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered, for example by 5 mg twice daily each week.

For patients unable to ingest tablets, Jakafi 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 nasogastric tube using an appropriate syringe.

The tube should be rinsed with approximately 75 mL of water. The effect of tube feeding preparations on Jakafi exposure during administration through a nasogastric tube has not been evaluated.

For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi 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 Jakafi. The effect of Jakafi 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.

5.3 Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi

Following discontinuation of Jakafi, 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 Jakafi: 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 Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia *[see Dosage and Administration (2.7)]*, consider tapering the dose of Jakafi gradually rather than discontinuing abruptly.

5.4 Non-Melanoma Skin Cancer (NMSC)

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations.

5.5 Lipid Elevations

Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides *[see Adverse Reactions (6.1)]*. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

Herpes Zoster[f]	2	0	0	< 1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Reactions

Anemia

In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy.

In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients.

Thrombocytopenia

In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50×10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in < 1% of patients receiving Jakafi and < 1% of patients receiving control regimens. Patients with a platelet count of 100×10^9/L to 200×10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200×10^9/L (17% versus 7%).

Neutropenia

In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia.

Table 13 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 13: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	< 1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-Controlled Study

- 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations.
- 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was < 1% for Jakafi with no Grade 3 or 4 AST elevations.
- 17% of patients treated with Jakafi and < 1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was < 1% for Jakafi with no Grade 3 or 4 cholesterol elevations.

Polycythemia Vera

In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy *[see Clinical Studies (13.2)]*. The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 14 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

Chronic Graft-Versus-Host Disease

In a Phase 3, randomized, open-label, multi-center study, 165 patients were treated with Jakafi and 158 patients were treated with best available therapy for cGVHD failing treatment with steroids with or without other immunosuppressive drugs *[see Clinical Studies (13.4)]*; sixty-five patients crossed over from best available therapy to treatment with Jakafi, for a total of 230 patients treated with Jakafi. The median duration of exposure to Jakafi for the study was 49.7 weeks (range, 0.7 to 144.9 weeks) in the Jakafi arm. One hundred and nine (47%) patients were on Jakafi for at least 1 year.

There were five fatal adverse reactions to Jakafi, including 1 from toxic epidermal necrolysis and 4 from neutropenia, anemia and/or thrombocytopenia. An adverse reaction resulting in treatment discontinuation occurred in 18% of patients treated with Jakafi. An adverse reaction resulting in dose modification occurred in 27%, and an adverse reaction resulting in treatment interruption occurred in 23%. The most common hematologic adverse reactions (incidence > 35%) are anemia and thrombocytopenia. The most common nonhematologic adverse reactions (incidence ≥ 20%) are infections (pathogen not specified) and viral infection.

Table 18 presents the most frequent nonlaboratory adverse reactions occurring up to Cycle 7 Day 1 of randomized treatment.

Table 18: Chronic Graft-Versus-Host Disease: All-Grade (≥ 10%) and Grades 3-5 (≥ 3%) Nonlaboratory Adverse Reactions Occurring in Patients in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

Adverse Reactions[b]	Jakafi (N = 165)		Best Available Therapy (N = 158)	
	All Grades[a] (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Infections and infestations				
Infections (pathogen not specified)	45	15	44	16
Viral infections	28	5	23	5
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	18	1	13	0
General disorders and administration site conditions				
Pyrexia	16	2	9	1
Fatigue	13	1	10	2
Edema	10	1	12	1
Vascular disorders				
Hypertension	16	5	13	7
Hemorrhage	12	2	15	2
Respiratory, thoracic and mediastinal disorders				
Cough	13	0	8	0
Dyspnea	11	1	8	1
Gastrointestinal disorders				
Nausea	12	0	13	2
Diarrhea	10	1	13	1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
[b] Grouped terms that are composites of applicable adverse reaction terms.

Clinically relevant laboratory abnormalities are shown in Table 19.

1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

8.4 Geriatric Use

Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients.

Clinical studies of Jakafi in patients with aGVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Of the total number of patients with cGVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients.

8.5 Renal Impairment

Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 to 59 mL/min) and severe (CLcr 15 to 29 mL/min) renal impairment, and ESRD (CLcr less than 15 mL/min) on dialysis *[see Clinical Pharmacology (11.3)]*. Modify Jakafi dosage as recommended *[see Dosage and Administration (2.6)]*.

8.6 Hepatic Impairment

Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment *[see Clinical Pharmacology (11.3)]*.

Reduce Jakafi dosage as recommended in patients with MF or PV with hepatic impairment *[see Dosage and Administration (2.6)]*. Reduce Jakafi dosage as recommended for patients with Stage 4 liver aGVHD.

Monitor blood counts more frequently for toxicity and modify the Jakafi dosage for adverse reactions if they occur for patients with Score 3 liver cGVHD *[see Dosage and Administration (2.6) and Clinical Pharmacology (11.3)]*.

10 OVERDOSAGE

There is no known antidote for overdoses with Jakafi. 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, anemia and thrombocytopenia. Appropriate supportive treatment should be given.

12.2 Pharmacodynamics

Jakafi inhibits cytokine induced STAT3 phosphorylation in whole blood from patients with MF and PV. STAT3 phosphorylation reached maximal inhibition 2 hours after Jakafi dosing and returned to near baseline by 10 hours in patients with MF and PV.

Cardiac Electrophysiology

At a dose of 1.25 to 10 times the highest recommended starting dosage, Jakafi does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Mean ruxolitinib maximal plasma concentration (C_{max}) and AUC increased proportionally over a single dose range of 5 mg to 200 mg (4 times the approved highest recommended total daily dosage of 25 mg twice daily). Mean ruxolitinib C_{max} ranged from 205 nM to 7100 nM and AUC ranged from 862 nM*hr to 30700 nM*hr over a single dose range of 5 mg to 200 mg.

Absorption

Ruxolitinib achieves C_{max} within 1 hour to 2 hours post-dose. Oral absorption of ruxolitinib is estimated to be at least 95%.

Effect of Food

No clinically relevant changes in the pharmacokinetics of ruxolitinib were observed upon administration of Jakafi with a high-fat, high-calorie meal (approximately 800 to 1000 calories of which 50% were derived from fat).

Distribution

The mean ruxolitinib volume of distribution at steady-state is 72 L (coefficient of variation [CV] 29%) in patients with MF and 75 L (23%) in patients with PV.

Protein binding of ruxolitinib is approximately 97%, mostly to albumin.

Elimination

The mean elimination half-life of ruxolitinib is approximately 3 hours and the mean elimination half-life of ruxolitinib and its metabolites is approximately 5.8 hours in healthy volunteers.

Ruxolitinib clearance (%CV) was 17.7 L/h in women and 22.1 L/h in men with MF (39%).

Ruxolitinib clearance (%CV) was 12.7 L/h (42%) in patients with PV.

Ruxolitinib clearance (%CV) was 11.8 L/h (63%) in patients with aGVHD.

Ruxolitinib clearance (%CV) was 9.7 L/h (51%) in patients with cGVHD.

Metabolism

Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Fluconazole: Fluconazole 100 to 400 mg once daily (a moderate CYP3A4 and CYP2C9 inhibitor) increases steady state ruxolitinib AUC by approximately 100% to 300% *[see Dosage and Administration (2.5) and Drug Interactions (7)]*.

Strong CYP3A4 inhibitors: Ketoconazole (strong CYP3A4 inhibitor) increased ruxolitinib C_{max} by 33% and AUC by 91% and prolonged ruxolitinib half-life from 3.7 hours to 6 hours *[see Dosage and Administration (2.5) and Drug Interactions (7)]*.

Moderate CYP3A4 inhibitors: Erythromycin (moderate CYP3A4 inhibitor) increased ruxolitinib C_{max} by 8% and AUC by 27% *[see Drug Interactions (7)]*.

Strong CYP3A4 inducers: Rifampin (strong CYP3A4 inducer) decreased ruxolitinib C_{max} by 32% and AUC by 61%. The relative exposure to ruxolitinib's active metabolites increased approximately 100% *[see Drug Interactions (7)]*.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Ruxolitinib and its M18 metabolite did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Ruxolitinib did not induce CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations.

Transporter Systems: Ruxolitinib and its M18 metabolite did not inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 at clinically relevant concentrations. Ruxolitinib was not a P-gp substrate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ruxolitinib was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model or in a 2-year carcinogenicity study in the rat.

Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in *in vitro* chromosomal aberration assay (cultured human peripheral blood lymphocytes) or *in vivo* in a rat bone marrow micronucleus assay.

In a fertility study, ruxolitinib was administered to male rats prior to and throughout mating and to female rats prior to mating and up to the implantation day (gestation day 7). Ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses of 10, 30 or 60 mg/kg/day. However, in female rats doses of greater than or equal to 30 mg/kg/day resulted in increased post-implantation loss. The exposure (AUC) at the dose of 30 mg/kg/day is approximately 34% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

14 CLINICAL STUDIES

14.1 Myelofibrosis

Two randomized Phase 3 studies (Studies 1 and 2) were conducted in patients with MF (either primary MF, post-polycythemia vera MF or post-essential thrombocythemia-MF). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate 2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group Consensus Criteria (IWG).

The starting dose of Jakafi was based on platelet count. Patients with a platelet count between 100 and 200 × 10^9/L were started on Jakafi 15 mg twice daily and patients with a platelet count greater than 200 × 10^9/L were started on Jakafi 20 mg twice daily. Doses were then individualized based upon tolerability and efficacy with maximum doses of 20 mg twice daily for patients with platelet counts between 100 to less than or equal to 125 × 10^9/L, of 10 mg twice daily for patients with platelet counts between 75 to less than or equal to 100 × 10^9/L, and of 5 mg twice daily for patients with platelet counts between 50 to less than or equal to 75 × 10^9/L.

Study 1

Study 1 (NCT00952289) was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The median age was 68 years (range 40 to 91 years) with 61% of patients older than 65 years and 54% were male. Fifty percent (50%) of patients had primary MF, 31% had post-polycythemia vera MF and 18% had post-essential thrombocythemia MF. Twenty-one percent (21%) of patients had red blood cell transfusions within 8 weeks of enrollment in the study. The median hemoglobin count was 10.5 g/dL and the median platelet count was 251 × 10^9/L. Patients had a median palpable spleen length of 16 cm below the costal margin, with 81% having a spleen length 10 cm or greater below the costal margin. Patients had a median spleen volume as measured by magnetic resonance imaging (MRI) or computed tomography (CT) of 2595 cm^3 (range 478 cm^3 to 8881 cm^3). (The upper limit of normal is approximately 300 cm^3).

Patients were dosed with Jakafi or matching placebo. The primary efficacy endpoint was the proportion of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume at Week 24 as measured by MRI or CT.

Secondary endpoints included duration of a 35% or greater reduction in spleen volume and proportion of patients with a 50% or greater reduction in Total Symptom Score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary.

Study 2

Study 2 (NCT00934544) was an open-label, randomized study in 219 patients. Patients were randomized 2:1 to Jakafi versus best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. In the best available therapy arm, the medications received by more than 10% of patients were hydroxyurea (47%) and glucocorticoids (16%). The median age was 66 years (range 35 to 85 years) with 52% of patients older than 65 years and 57% were male. Fifty-three percent (53%) of patients had primary MF, 31% had post-

Thrombocytopenia, Anemia and Neutropenia

Inform patients that Jakafi is associated with thrombocytopenia, anemia and neutropenia, and of the need to monitor complete blood counts before and during treatment. Advise patients to observe for and report bleeding *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients of the signs and symptoms of infection and to report any such signs and symptoms promptly.

Inform patients regarding the early signs and symptoms of herpes zoster and of progressive multifocal leukoencephalopathy, and advise patients to seek advice of a clinician if such symptoms are observed *[see Warnings and Precautions (5.2)]*.

Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi

Inform patients that after discontinuation of treatment, signs and symptoms from myeloproliferative neoplasms are expected to return. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician *[see Warnings and Precautions (5.3)]*.

Non-Melanoma Skin Cancer

Inform patients that Jakafi may increase their risk of certain non-melanoma skin cancers. Advise patients to inform their healthcare provider if they have ever had any type of skin cancer or if they observe any new or changing skin lesions *[see Warnings and Precautions (5.4)]*.

Lipid Elevations

Inform patients that Jakafi may increase blood cholesterol, and of the need to monitor blood cholesterol levels *[see Warnings and Precautions (5.5)]*.

Major Adverse Cardiovascular Events (MACE)

Advise patients that events of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death, have been reported in clinical studies with another JAK-inhibitor used to treat rheumatoid arthritis, a condition for which Jakafi is not indicated. Advise patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions (5.6)]*.

Thrombosis

Advise patients that events of DVT and PE have been reported in clinical studies with another JAK-inhibitor used to treat rheumatoid arthritis, a condition for which Jakafi is not indicated. Advise patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.7)]*.

Secondary Malignancies

Advise patients, especially current or past smokers and patients with a known secondary malignancy (other than a successfully treated NMSC), that lymphoma and other malignancies

(excluding NMSC) have been reported in clinical studies with another JAK-inhibitor used to treat rheumatoid arthritis, a condition for which Jakafi is not indicated *[see Warnings and Precautions (5.8)]*.

Drug-Drug Interactions

Advise patients to inform their healthcare providers of all medications they are taking, including over-the-counter medications, herbal products and dietary supplements *[see Drug Interactions (7.1) and Clinical Pharmacology (11.3)]*.

Dialysis

Inform patients on dialysis that their dose should not be taken before dialysis but only following dialysis *[see Dosage and Administration (2.6)]*.

Lactation

Inform women not to breastfeed during treatment with Jakafi and for two weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Compliance

Advise patients to continue taking Jakafi every day for as long as their physician tells them and that this is a long-term treatment. Patients should not change dose or stop taking Jakafi without first consulting their physician. Patients should be aware that after discontinuation of treatment, signs and symptoms from myeloproliferative neoplasms are expected to return.

Manufactured for:
Incyte Corporation
1801 Augustine Cut-off
Wilmington, DE 19803

Patient Information
JAKAFI® (JAK-ah-fye)
(ruxolitinib)
tablets

What is Jakafi?

Jakafi is a prescription medicine used to treat:

- adults with certain types of myelofibrosis (MF).
- adults with polycythemia vera (PV) who have already taken a medicine called hydroxyurea and it did not work well enough or they could not tolerate it.
- adults and children 12 years of age and older with acute graft-versus-host-disease (aGVHD) who have taken corticosteroids and they did not work well enough.
- adults and children 12 years of age and older with chronic graft-versus-host-disease (cGVHD) who have taken one or two types of treatments and they did not work well enough.

It is not known if Jakafi is safe or effective in children for treatment of myelofibrosis or polycythemia vera.

Before taking Jakafi, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection
- have or have had low white or red blood cell counts
- have or had tuberculosis (TB), or have been in close contact with someone who has TB
- have had shingles (herpes zoster)
- have or had hepatitis B
- have or have had liver problems
- have or have had kidney problems or are on dialysis. If you are on dialysis, Jakafi should be taken after your dialysis.
- have a high level of fat in your blood (high blood cholesterol or triglycerides)
- have had cancer in the past
- are a current or past smoker
- have had a blood clot, heart attack, other heart problems or stroke
- are pregnant or plan to become pregnant. It is not known if Jakafi will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Jakafi passes into your breast milk. Do not breastfeed during treatment with Jakafi and for 2 weeks after the final dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Taking Jakafi with certain other medicines may affect how Jakafi works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Jakafi?

- Take Jakafi exactly as your healthcare provider tells you.
- Do not change your dose or stop taking Jakafi without first talking to your healthcare provider.
- You can take Jakafi with or without food.
- Jakafi may also be given through certain nasogastric tubes.
  - Tell your healthcare provider if you cannot take Jakafi by mouth. Your healthcare provider will decide if you can take Jakafi through a nasogastric tube.
  - Ask your healthcare provider to give you specific instruction on how to properly take Jakafi through a nasogastric tube.
- If you miss a dose of Jakafi, take your next dose at your regular time. Do not take 2 doses at the same time.
- If you take too much Jakafi call your healthcare provider or go to the nearest hospital emergency room right away.
- You will have regular blood tests during your treatment with Jakafi. Your healthcare provider may change your dose of Jakafi or stop your treatment based on the results of your blood tests.

What are the possible side effects of Jakafi?

Jakafi can cause serious side effects including:

Low blood cell counts. Jakafi may cause low platelet counts (thrombocytopenia), low red blood cell counts (anemia), and low white blood cell counts (neutropenia). If you develop bleeding, stop Jakafi and call your healthcare provider. Your healthcare provider will do a blood test to check your blood cell counts before you start Jakafi and regularly during

your treatment with Jakafi. Tell your healthcare provider right away if you develop or have worsening of any of these symptoms:

- unusual bleeding
- bruising
- tiredness
- shortness of breath
- fever

Infection. You may be at risk for developing a serious infection during treatment with Jakafi. Tell your healthcare provider if you develop any of the following symptoms of infection:

- chills
- aches
- fever
- nausea
- vomiting
- weakness
- painful skin rash or blisters

Cancer. Some people have had certain types of non-melanoma skin cancers during treatment with Jakafi. Your healthcare provider will regularly check your skin during your treatment with Jakafi. Tell your healthcare provider if you develop any new or changing skin lesions during treatment with Jakafi.

Cholesterol increases. You may have changes in your blood cholesterol levels during treatment with Jakafi. Your healthcare provider will do blood tests to check your cholesterol levels about every 8 to 12 weeks after you start taking Jakafi, and as needed.

Increased risk of major cardiovascular events such as heart attack, stroke or death in people who have cardiovascular risk factors and who are current or past smokers while using another JAK inhibitor to treat rheumatoid arthritis.

Get emergency help right away if you have any symptoms of a heart attack or stroke while taking Jakafi, including:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded
- weakness in one part or on one side of your body
- slurred speech

Increased risk of blood clots. Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) have happened in people taking another JAK inhibitor for rheumatoid arthritis and may be life-threatening.

- Tell your healthcare provider right away if you have any signs and symptoms of blood clots during treatment with Jakafi, including:
  - swelling, pain or tenderness in one or both legs
  - sudden, unexplained chest or upper back pain
  - shortness of breath or difficulty breathing

Possible increased risk of new (secondary) cancers. People who take another JAK inhibitor for rheumatoid arthritis have an increased risk of new (secondary) cancers, including lymphoma and other cancers. People who smoke or who smoked in the past have an added risk of new cancers.

The most common side effects of Jakafi in adults with certain types of MF and PV include:

- low platelet counts
- low red blood cell counts
- bruising
- dizziness
- headache
- diarrhea

The most common side effects of Jakafi in people with aGVHD include:

- low red blood cell counts
- low platelet counts
- low white blood cell counts
- infections
- swelling

The most common side effects of Jakafi in people with cGVHD include:

- low red blood cell counts
- low platelet counts
- infections, including viral infections

These are not all of the possible side effects of Jakafi.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Incyte Corporation at 1-855-463-3463.

How should I store Jakafi?

- Store Jakafi at room temperature 68°F to 77°F (20°C to 25°C).

Keep Jakafi and all medicines out of the reach of children.

General information about the safe and effective use of Jakafi.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use Jakafi for a condition for which it is not prescribed. Do not give Jakafi to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information that is written for healthcare professionals.

What are the ingredients in Jakafi?

Active ingredient: ruxolitinib phosphate

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose

Manufactured for: Incyte Corporation, 1801 Augustine Cut-off, Wilmington, DE 19803

U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 8829013; 9079912; 9814722; 10016429

For more information call 1-855-463-3463 or go to www.jakafi.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: September 2021