HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JAKAFI safely and effectively. See full prescribing information for JAKAFI.

JAKAFI® (ruxolitinib) tablets, for oral use
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Warnings and Precautions (5.2) 10/2017

INDICATIONS AND USAGE

Jakafi is a kinase inhibitor indicated for treatment of patients with:

- intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. (1.1)
- polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. (1.2)

DOSAGE AND ADMINISTRATION

Doses should be individualized based on safety and efficacy. Starting doses per indication are noted below.

Myelofibrosis (2.1)

- The starting dose of Jakafi is based on patient's baseline platelet count:
  - Greater than 200 X 10^9/L: 20 mg given orally twice daily
  - 100 X 10^9/L to 200 X 10^9/L: 15 mg given orally twice daily
  - 50 X 10^9/L to less than 100 X 10^9/L: 5 mg given orally twice daily
- Monitor complete blood counts every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Modify or interrupt dosing for thrombocytopenia.

Polycythemia Vera (2.2)

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

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg, 15 mg, 20 mg and 25 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Thrombocytopenia, Anemia and Neutropenia: Manage by dose reduction, or interruption, or transfusion. (5.1)
- Risk of Infection: Assess patients for signs and symptoms of infection and initiate appropriate treatment promptly. Serious infections should have resolved before starting therapy with Jakafi. (5.2)
- Symptom Exacerbation Following Interruption or Discontinuation: Manage with supportive care and consider resuming treatment with Jakafi. (5.3)
- Risk of Non-Melanoma Skin Cancer: Perform periodic skin examinations. (5.4)
- Lipid Elevations: Assess lipid levels 8-12 weeks from start of therapy and treat as needed. (5.5)

ADVERSE REACTIONS

The most common hematologic adverse reactions (incidence > 20%) are thrombocytopenia and anemia. The most common non-hematologic adverse reactions (incidence >10%) are bruising, dizziness and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Incyte Corporation at 1-855-463-3463 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors or Fluconazole: Reduce, interrupt, or discontinue Jakafi doses as recommended. Avoid use of Jakafi with fluconazole doses greater than 200 mg. (2.3) (7.1)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Reduce Jakafi starting dose or avoid treatment as recommended. (2.4) (8.6)
- Hepatic Impairment: Reduce Jakafi starting dose or avoid treatment as recommended. (2.4) (8.7)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Myelofibrosis

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

1.2 Polycythemia Vera

Jakafi is indicated for treatment of patients with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea.

2 DOSAGE AND ADMINISTRATION

2.1 Myelofibrosis

The recommended starting dose of Jakafi is based on platelet count (Table 1). A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Warnings and Precautions (5.1)*]. Doses may be titrated based on safety and efficacy.

Table 1: Jakafi Starting Doses for Myelofibrosis

Platelet Count	Starting Dose
Greater than 200 X 10^9/L	20 mg orally twice daily
100 X 10^9/L to 200 X 10^9/L	15 mg orally twice daily
50 X 10^9/L to less than 100 X 10^9/L	5 mg orally twice daily

2.1.1 Dose Modification Guidelines for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

Treatment Interruption and Restarting Dosing

Interrupt treatment for platelet counts less than 50 X 10^9/L or absolute neutrophil count (ANC) less than 0.5 X 10^9/L.

After recovery of platelet counts above 50 X 10^9/L and ANC above 0.75 X 10^9/L, dosing may be restarted. Table 2 illustrates the maximum allowable dose that may be used in restarting Jakafi after a previous interruption.

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Table 2: Myelofibrosis: Maximum Restarting Doses for Jakafi after Safety Interruption for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

Current Platelet Count	Maximum Dose When Restarting Jakafi Treatment*
Greater than or equal to 125 X 10^9/L	20 mg twice daily
100 to less than 125 X 10^9/L	15 mg twice daily
75 to less than 100 X 10^9/L	10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
50 to less than 75 X 10^9/L	5 mg twice daily for at least 2 weeks; if stable, may increase to 10 mg twice daily
Less than 50 X 10^9/L	Continue hold

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

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

Dose Reductions

Dose reductions should be considered if the platelet counts decrease as outlined in Table 3 with the goal of avoiding dose interruptions for thrombocytopenia.

Table 3: Myelofibrosis: Dosing Recommendations for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

	Dose at Time of Platelet Decline				
Platelet Count	**25 mg twice daily**	**20 mg twice daily**	**15 mg twice daily**	**10 mg twice daily**	**5 mg twice daily**
	New Dose	**New Dose**	**New Dose**	**New Dose**	**New Dose**
100 to less than 125 X 10^9/L	20 mg twice daily	15 mg twice daily	No Change	No Change	No Change
75 to less than 100 X 10^9/L	10 mg twice daily	10 mg twice daily	10 mg twice daily	No Change	No Change
50 to less than 75 X 10^9/L	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No Change
Less than 50 X 10^9/L	Hold	Hold	Hold	Hold	Hold

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2.1.2 Dose Modification Based on Insufficient Response for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

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

a. 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);
b. Platelet count greater than 125 X 10^9/L at 4 weeks and platelet count never below 100 X 10^9/L;
c. ANC Levels greater than 0.75 X 10^9/L.

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

2.1.3 Dose Modifications for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with Platelet Counts of 50 X 10^9/L to Less Than 100 X 10^9/L

This section applies only to patients with platelet counts of 50 X 10^9/L to less than 100 X 10^9/L prior to any treatment with Jakafi. See Section 2.1.1 for dose modifications for hematological toxicity in patients whose platelet counts were 100 X 10^9/L or more prior to starting treatment with Jakafi.

Treatment Interruption and Restarting Dosing

Interrupt treatment for platelet counts less than 25 X 10^9/L or ANC less than 0.5 X 10^9/L.

After recovery of platelet counts above 35 X 10^9/L and ANC above 0.75 X 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 X 10^9/L or ANC below 0.5 X 10^9/L that led to dose interruption.

Dose Reductions

Reduce the dose of Jakafi for platelet counts less than 35 X 10^9/L as described in Table 4.

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Table 4: Myelofibrosis: Dosing Modifications for Thrombocytopenia for Patients with Starting Platelet Count of 50 X 10^9/L to Less Than 100 X 10^9/L

Platelet Count	Dosing Recommendations
Less than 25 X 10^9/L	• Interrupt dosing.
25 X 10^9/L to less than 35 X 10^9/L AND the platelet count decline is less than 20% during the prior four weeks	• Decrease dose by 5 mg once daily. • For patients on 5 mg once daily, maintain dose at 5 mg once daily.
25 X 10^9/L to less than 35 X 10^9/L AND the platelet count decline is 20% or greater during the prior four weeks	• Decrease dose by 5 mg twice daily. • For patients on 5 mg twice daily, decrease the dose to 5 mg once daily. • For patients on 5 mg once daily, maintain dose at 5 mg once daily.

2.1.4 Dose Modifications Based on Insufficient Response for Patients with Myelofibrosis and Starting Platelet Count of 50 X 10^9/L to Less Than 100 X 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 as defined in Section 2.1.2, doses may be increased by increments of 5 mg daily to a maximum of 10 mg twice daily if:

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

2.1.5 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 Jakafi at a lower dose.

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2.2 Polycythemia Vera

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

2.2.1 Dose Modification Guidelines for Patients with Polycythemia Vera

A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Warnings and Precautions (5.1)*].

Dose Reductions

Dose reductions should be considered for hemoglobin and platelet count decreases as described in Table 5.

Table 5: Polycythemia Vera: Dose Reductions

Hemoglobin and/or Platelet Count	Dosing Recommendations
Hemoglobin greater than or equal to 12 g/dL AND platelet count greater than or equal to 100 X 10^9/L	• No change required.
Hemoglobin 10 to less than 12 g/dL AND platelet count 75 to less than 100 X 10^9/L	• Dose reductions should be considered with the goal of avoiding dose interruptions for anemia and thrombocytopenia.
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 X 10^9/L	• Reduce dose by 5 mg twice daily. • For patients on 5 mg twice daily, decrease the dose to 5 mg once daily.
Hemoglobin less than 8 g/dL OR platelet count less than 50 X 10^9/L	• Interrupt dosing.

Treatment Interruption and Restarting Dosing

Interrupt treatment for hemoglobin less than 8 g/dL, platelet counts less than 50 X 10^9/L or ANC less than 1.0 X 10^9/L.

After recovery of the hematologic parameter(s) to acceptable levels, dosing may be restarted.

Table 6 illustrates the dose that may be used in restarting Jakafi after a previous interruption.

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Table 6: Polycythemia Vera: Restarting Doses for Jakafi 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 X 10^9/L OR ANC less than 1 X 10^9/L	Continue hold
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 X 10^9/L OR ANC 1 to less than 1.5 X 10^9/L	5 mg twice daily[a] or no more than 5 mg twice daily 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 X 10^9/L OR ANC 1.5 to less than 2 X 10^9/L	10 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin greater than or equal to 12 g/dL OR platelet count greater than or equal to 100 X 10^9/L OR ANC greater than or equal to 2 X 10^9/L	15 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption

[a] 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 twice daily, may restart at a dose of 5 mg twice daily or 5 mg once daily, but not higher, once hemoglobin is greater than or equal to 10 g/dL, platelet count is greater than or equal to 75 X 10^9/L, and ANC is greater than or equal to 1.5 X 10^9/L.

Dose Management after Restarting Treatment

After restarting Jakafi 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 Jakafi would not be limited.

2.2.2 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 twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every two weeks.

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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 X 10^9/L
3. Hemoglobin greater than or equal to 12 g/dL
4. ANC greater than or equal to 1.5 X 10^9/L

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

Modify the Jakafi dosage when coadministered with strong CYP3A4 inhibitors and fluconazole doses of less than or equal to 200 mg [*see Drug Interactions (7.1)*], according to Table 7.

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

Avoid the use of fluconazole doses of greater than 200 mg daily with Jakafi.

Table 7: Dose Modifications for Concomitant Use of Strong CYP3A4 Inhibitors or Fluconazole

For patients coadministered strong CYP3A4 inhibitors or fluconazole doses of less than or equal to 200 mg	**Recommended Dose Modification**
Starting dose for patients with MF with a platelet count:	
• Greater than or equal to 100 X 10^9/L	10 mg twice daily
• 50 X 10^9/L to less than 100 X 10^9/L	5 mg once daily
Starting dose for patients with PV:	5 mg twice daily
If on stable dose for patients with 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

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2.4 Dose Modifications for Organ Impairment

Renal Impairment

Patients with Moderate or Severe Renal Impairment

Modify the Jakafi dosage for patients with moderate or severe renal impairment according to Table 8.

Table 8: Dose Modifications for Renal Impairment

Renal Impairment Status	Platelet Count	Recommended Starting Dosage
Patients with MF Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Greater than 150 X 10^9/L	No dose modification needed
	100 X 10^9/L to 150 X 10^9/L	10 mg twice daily
	50 to less than 100 X 10^9/L	5 mg daily
	Less than 50 X 10^9/L	Avoid use [*see Use in Specific Populations (8.6)*]
Patients with PV Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Any	5 mg twice daily

Patients with End Stage Renal Disease on Dialysis

The recommended starting dose for patients with MF with end stage renal disease (ESRD) on dialysis is 15 mg once after a dialysis session for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L or 20 mg once after a dialysis session for patients with a platelet count of greater than 200 X 10^9/L.

The recommended starting dose for patients with PV with ESRD on dialysis is 10 mg.

Make additional dose modifications with frequent monitoring of safety and efficacy. Avoid use of Jakafi in patients with ESRD (CLcr less than 15 mL/min) not requiring dialysis [*see Use in Specific Populations (8.6)*].

Hepatic Impairment

Modify the Jakafi 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 X 10^9/L	No dose modification needed
	100 X 10^9/L to 150 X 10^9/L	10 mg twice daily
	50 to less than 100 X 10^9/L	5 mg daily
	Less than 50 X 10^9/L	Avoid use [*see Use in Specific Populations (8.7)*]

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Patients with PV Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Any	5 mg twice daily

2.5 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.

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3 DOSAGE FORMS AND STRENGTHS

5 mg tablets - round and white with “INCY” on one side and “5” on the other.

10 mg tablets - round and white with “INCY” on one side and “10” on the other.

15 mg tablets - oval and white with “INCY” on one side and “15” on the other.

20 mg tablets - capsule-shaped and white with “INCY” on one side and “20” on the other.

25 mg tablets - oval and white with “INCY” on one side and “25” on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia, Anemia and Neutropenia

Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1)*].

Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1), and Adverse Reactions (6.1)*].

Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.

Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1)*].

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. [*see Dosage and Administration (2.1.1), and Adverse Reactions (6.1)*].

5.2 Risk of Infection

Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly.

Tuberculosis

Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly.

Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a

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person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed.

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 [*see Adverse Reactions (6.1*)].

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 (2.5)*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly.

5.4 Non-Melanoma Skin Cancer

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. 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

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initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1)*]
- Risk of Infection [*see Warnings and Precautions (5.2)*]
- Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3)*]
- Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience in Myelofibrosis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies.

In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy.

In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 11*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 10*].

Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo.

Table 10 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

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Table 10: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
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 Drug 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 X 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

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receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 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 X 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 11 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 11: 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.

6.2 Clinical Trial Experience in 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 (14.2)]*. The most frequent adverse drug reaction was anemia. Table 12 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32.

Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

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Table 12: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were:

Weight gain, hypertension, and urinary tract infections

Clinically relevant laboratory abnormalities are shown in Table 13.

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Table 13: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

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

7 DRUG INTERACTIONS

Fluconazole

Concomitant administration of Jakafi with fluconazole doses greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways [*see Clinical Pharmacology (12.3)*]. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3)*].

Strong CYP3A4 inhibitors

Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure [*see Clinical Pharmacology (12.3)*]. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors [*see Dosage and Administration (2.3)*].

Strong CYP3A4 inducers

Concomitant administration of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [*see Clinical Pharmacology (12.3)*]. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Clinical Pharmacology (12.3)*].

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity (*see Data*). There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose.

In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily).

8.2 Lactation

Risk Summary

No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed infant, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats (*see Data*). Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose.

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Data

Animal Data

Lactating rats were administered a single dose of [^{14}C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

8.4 Pediatric Use

The safety and effectiveness of Jakafi in pediatric patients have not been established.

8.5 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.

8.6 Renal Impairment

Reduce the Jakafi dosage when administering Jakafi to patients with MF and moderate (CLcr 30 mL/min to 59 mL/min as estimated using Cockcroft-Gault) or severe renal impairment (CLcr 15 mL/min to 29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

Reduce the Jakafi dosage for patients with PV and moderate (CLcr 30 to 59 mL/min) or severe renal impairment (CLcr 15 to 29 mL/min) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

Reduce the Jakafi dosage for all patients with ESRD on dialysis [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Reduce the Jakafi dosage when administering Jakafi to patients with MF and any degree of hepatic impairment (Child-Pugh Class A, B and C) and with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

Reduce the Jakafi dosage for patients with PV and hepatic impairment (Child-Pugh Class A, B and C) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

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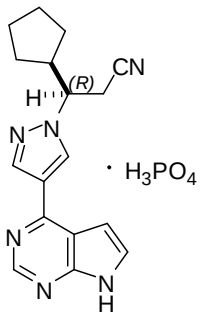
10 OVERDOSAGE

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.

Hemodialysis is not expected to enhance the elimination of Jakafi.

11 DESCRIPTION

Ruxolitinib phosphate is a kinase inhibitor with the chemical name (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36. Ruxolitinib phosphate has the following structural formula:



Ruxolitinib phosphate is a white to off-white to light pink powder and is soluble in aqueous buffers across a pH range of 1 to 8.

Jakafi (ruxolitinib) Tablets are for oral administration. Each tablet contains ruxolitinib phosphate equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

MF and PV are myeloproliferative neoplasms (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen and decreased circulating inflammatory cytokines (e.g., TNF-α, IL-6).

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12.2 Pharmacodynamics

Jakafi inhibits cytokine induced STAT3 phosphorylation in whole blood from patients with MF and PV. Jakafi administration resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which 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 C_{max} and AUC increased proportionally over a single dose range of 5 mg to 200 mg. 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 maximal plasma concentration (C_{max}) within 1 hour to 2 hours post-dose. Oral absorption of ruxolitinib is estimated to be at least 95%.

Food Effect

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 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.

Binding to plasma proteins is approximately 97%, mostly to albumin.

Elimination

The mean elimination half-life of ruxolitinib is approximately 3 hours and the mean half-life of ruxolitinib + metabolites is approximately 5.8 hours.

Ruxolitinib clearance was 17.7 L/h in women and 22.1 L/h in men with MF (39% inter-subject variability).

Ruxolitinib clearance was 12.7 L/h in patients with PV (42% inter-subject variability).

Metabolism

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

Excretion

Following a single oral dose of radiolabeled ruxolitinib, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity.

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Specific Populations

No clinically relevant differences in ruxolitinib pharmacokinetics were observed with regard to age, race, sex, or weight.

Patients with Renal Impairment

The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CLcr 72 mL/min to 164 mL/min as estimated using Cockcroft-Gault] and in subjects with mild [CLcr 53 mL/min to 83 mL/min], moderate [CLcr 38 mL/min to 57 mL/min], or severe renal impairment [CLcr 15 mL/min to 51 mL/min]. Additional subjects with ESRD requiring hemodialysis were also enrolled.

The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function, but the plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with ESRD requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out.

Patients with Hepatic Impairment

The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects and in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C]. The mean AUC for ruxolitinib was increased by 87% in patients with mild impairment, 28% in patients with moderate impairment and 65% in patients with severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy subjects (4.1 hours to 5 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib.

Drug Interactions

Fluconazole

Simulations suggest that fluconazole (a dual CYP3A4 and CYP2C9 inhibitor) increases steady state ruxolitinib AUC by approximately 100% to 300% following concomitant administration of 10 mg of Jakafi twice daily with 100 mg to 400 mg of fluconazole once daily [*see Dosage and Administration (2.3) and Drug Interactions (7)*].

Strong CYP3A4 inhibitors

Ketoconazole (a strong CYP3A4 inhibitor) increased ruxolitinib C_{max} by 33% and AUC by 91%. Ketoconazole also prolonged ruxolitinib half-life from 3.7 hours to 6 hours [*see Dosage and Administration (2.3) and Drug Interactions (7)*].

Moderate CYP3A4 inhibitors

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

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Strong CYP3A4 inducers

Rifampin (a 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 (7.1)*].

In vitro studies

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.

Ruxolitinib and its M18 metabolite did not inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transport systems at clinically relevant concentrations. Ruxolitinib is not a substrate for the P-gp transporter.

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 X 10^9/L were started on Jakafi 15 mg twice daily and patients with a platelet count greater than 200 X 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

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for patients with platelet counts between 100 to less than or equal to 125 X 10^9/L, of 10 mg twice daily for patients with platelet counts between 75 to less than or equal to 100 X 10^9/L, and of 5 mg twice daily for patients with platelet counts between 50 to less than or equal to 75 X 10^9/L.

Study 1

Study 1 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 X 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 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-polycythemia vera MF and 16% 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 10.4 g/dL and the median platelet count was 236 X 10^9/L. Patients had a median palpable spleen length of 15 cm below the costal margin, with 70% having a spleen length 10 cm or greater below the costal margin. Patients had a median spleen volume as measured by MRI or CT of 2381 cm^3 (range 451 cm^3 to 7765 cm^3).

The primary efficacy endpoint was the proportion of patients achieving 35% or greater reduction from baseline in spleen volume at Week 48 as measured by MRI or CT.

A secondary endpoint in Study 2 was the proportion of patients achieving a 35% or greater reduction of spleen volume as measured by MRI or CT from baseline to Week 24.

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Study 1 and 2 Efficacy Results

Efficacy analyses of the primary endpoint in Studies 1 and 2 are presented in Table 14 below. A significantly larger proportion of patients in the Jakafi group achieved a 35% or greater reduction in spleen volume from baseline in both studies compared to placebo in Study 1 and best available therapy in Study 2. A similar proportion of patients in the Jakafi group achieved a 50% or greater reduction in palpable spleen length.

Table 14: Percent of Patients with Myelofibrosis Achieving 35% or Greater Reduction from Baseline in Spleen Volume at Week 24 in Study 1 and at Week 48 in Study 2 (Intent to Treat)

	Study 1		**Study 2**	
	Jakafi (N=155)	**Placebo (N=154)**	**Jakafi (N=146)**	**Best Available Therapy (N=73)**
Time Points	Week 24		Week 48	
Number (%) of Patients with Spleen Volume Reduction by 35% or More	65 (42)	1 (<1)	41 (29)	0
P-value	< 0.0001		< 0.0001	

Figure 1 shows the percent change from baseline in spleen volume for each patient at Week 24 (Jakafi N=139, placebo N=106) or the last evaluation prior to Week 24 for patients who did not complete 24 weeks of randomized treatment (Jakafi N=16, placebo N=47). One (1) patient (placebo) with a missing baseline spleen volume is not included.

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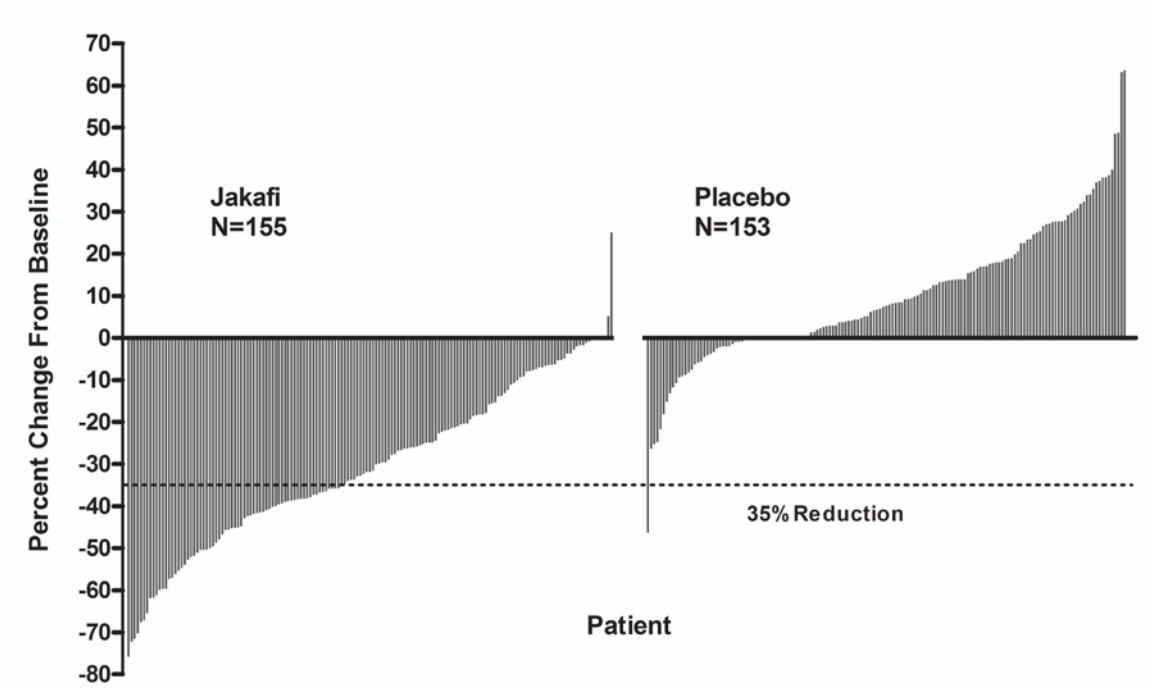
Figure 1: Percent Change from Baseline in Spleen Volume at Week 24 or Last Observation for Each Patient (Study 1)



In Study 1, MF symptoms were a secondary endpoint and were measured using the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary. The modified MFSAF is a daily diary capturing the core symptoms of MF (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety). Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60.

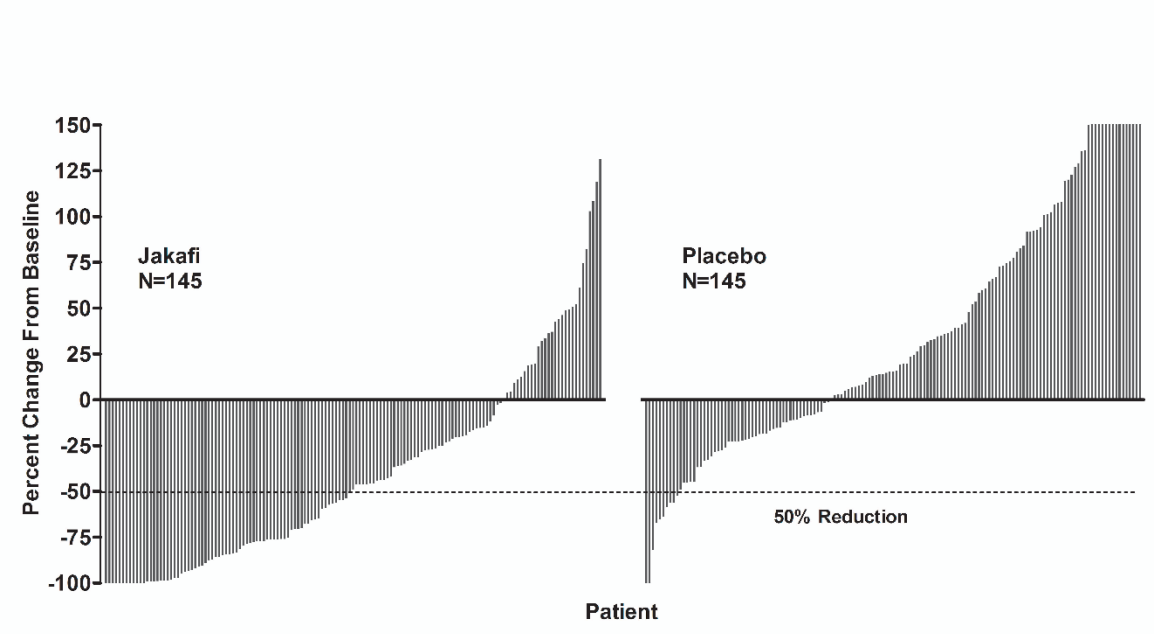
Table 15 presents assessments of Total Symptom Score from baseline to Week 24 in Study 1 including the proportion of patients with at least a 50% reduction (ie, improvement in symptoms). At baseline, the mean Total Symptom Score was 18.0 in the Jakafi group and 16.5 in the placebo group. A higher proportion of patients in the Jakafi group had a 50% or greater reduction in Total Symptom Score than in the placebo group, with a median time to response of less than 4 weeks.

Table 15: Improvement in Total Symptom Score in Patients with Myelofibrosis

	Jakafi (N=148)	**Placebo (N=152)**
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (46)	8 (5)
P-value	< 0.0001	

Figure 2 shows the percent change from baseline in Total Symptom Score for each patient at Week 24 (Jakafi N=129, placebo N=103) or the last evaluation on randomized therapy prior to Week 24 for patients who did not complete 24 weeks of randomized treatment (Jakafi N=16, placebo N=42). Results are excluded for 5 patients with a baseline Total Symptom Score of zero, 8 patients with missing baseline and 6 patients with insufficient post-baseline data.

Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)



Worsening of Total Symptom Score is truncated at 150%.

Figure 3 displays the proportion of patients with at least a 50% improvement in each of the individual symptoms that comprise the Total Symptom Score indicating that all 6 of the symptoms contributed to the higher Total Symptom Score response rate in the group treated with Jakafi.

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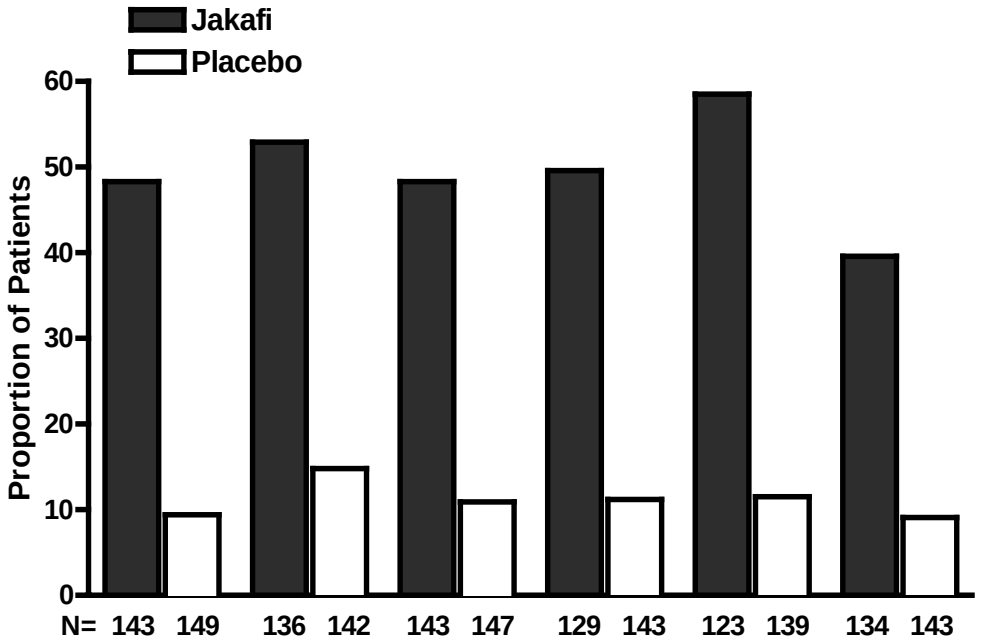
Figure 3: Proportion of Patients With Myelofibrosis Achieving 50% or Greater Reduction in Individual Symptom Scores at Week 24



	Abdominal discomfort		Pain under left ribs		Early satiety		Night sweats		Itching		Bone or muscle pain	
N=	143	149	136	142	143	147	129	143	123	139	134	143
Baseline Mean	3.9	3.6	2.9	2.6	3.9	3.6	3.2	2.6	2.8	2.6	3.3	2.8
Baseline Median	3.9	3.3	2.7	1.8	4.0	3.3	3.0	2.2	2.5	1.8	3.1	2.1

Individual score range = 0 to 10

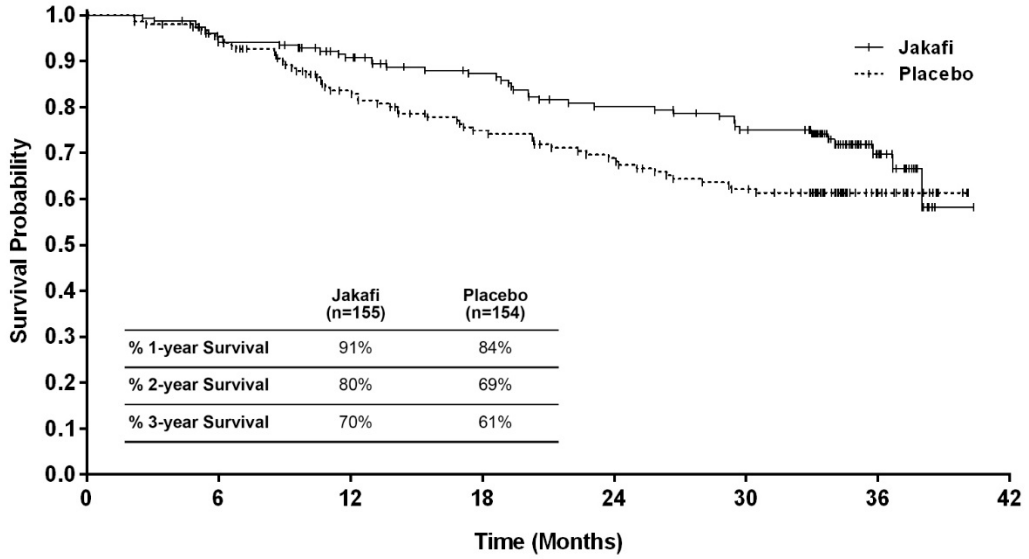
An exploratory analysis of patients receiving Jakafi also showed improvement in fatigue-related symptoms (i.e., tiredness, exhaustion, mental tiredness, and lack of energy) and associated impacts on daily activities (i.e., activity limitations related to work, self-care, and exercise) as measured by the PROMIS® Fatigue 7-item short form total score at Week 24. Patients who achieved a reduction of 4.5 points or more from baseline to Week 24 in the PROMIS® Fatigue total score were considered to have achieved a fatigue response. Fatigue response was reported in 35% of patients in the Jakafi group versus 14% of the patients in the placebo group.

Overall survival was a secondary endpoint in both Study 1 and Study 2. Patients in the control groups were eligible for crossover in both studies, and the median times to crossover were 9 months in Study 1 and 17 months in Study 2.

Figure 4 and Figure 5 show Kaplan-Meier curves of overall survival at prospectively planned analyses after all patients remaining on study had completed 144 weeks on study.

Reference ID: 4165150

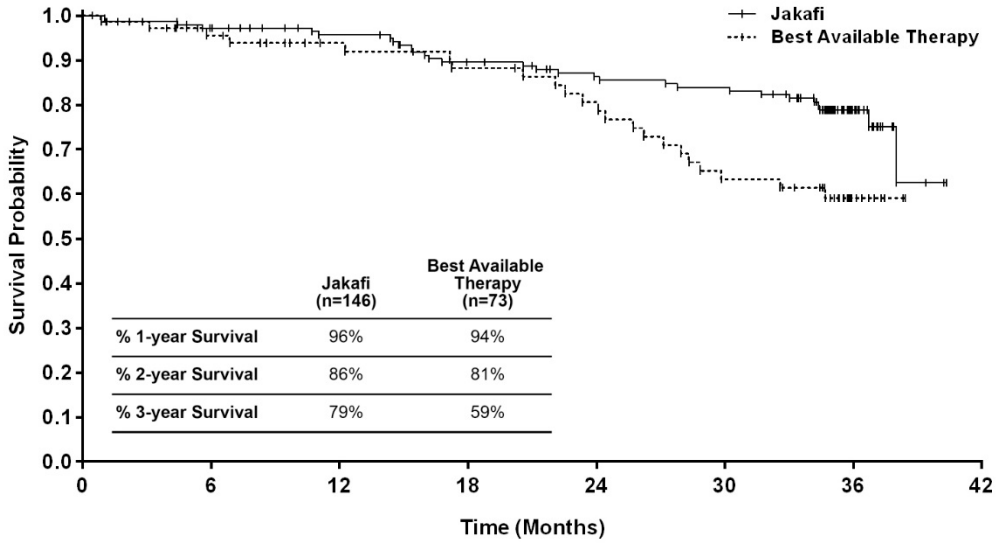
Figure 4: Overall Survival - Kaplan-Meier Curves by Treatment Group in Study 1



	Jakafi (n=155)	Placebo (n=154)
% 1-year Survival	91%	84%
% 2-year Survival	80%	69%
% 3-year Survival	70%	61%

Number at Risk:								
Jakafi	155	145	134	122	111	102	29	0
Placebo	154	142	117	101	92	82	32	0

Figure 5: Overall Survival - Kaplan-Meier Curves by Treatment Group in Study 2



	Jakafi (n=146)	Best Available Therapy (n=73)
% 1-year Survival	96%	94%
% 2-year Survival	86%	81%
% 3-year Survival	79%	59%

Number at Risk:								
Jakafi	146	135	126	115	107	104	33	0
Best Available Therapy	73	58	50	47	42	33	9	0

Reference ID: 4165150

14.2 Polycythemia Vera

Study 3 was a randomized, open-label, active-controlled Phase 3 study conducted in 222 patients with PV. Patients had been diagnosed with PV for at least 24 weeks, had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy and exhibited splenomegaly. All patients were required to demonstrate hematocrit control between 40-45% prior to randomization. The age ranged from 33 to 90 years with 30% of patients over 65 years of age and 66% were male. Patients had a median spleen volume as measured by MRI or CT of 1272 cm^3 (range 254 cm^3 to 5147 cm^3) and median palpable spleen length below the costal margin was 7 cm.

Patients were randomized to Jakafi or best available therapy. The starting dose of Jakafi was 10 mg twice daily. Doses were then individualized based upon tolerability and efficacy with a maximum dose of 25 mg twice daily. At Week 32, 98 patients were still on Jakafi with 8% receiving greater than 20 mg twice daily, 15% receiving 20 mg twice daily, 33% receiving 15 mg twice daily, 34% receiving 10 mg twice daily, and 10% receiving less than 10 mg twice daily. Best available therapy (BAT) was selected by the investigator on a patient-by-patient basis and included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%).

The primary endpoint was the proportion of subjects achieving a response at Week 32, with response defined as having achieved both hematocrit control (the absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32) and spleen volume reduction (a greater than or equal to 35% reduction from baseline in spleen volume at Week 32). Phlebotomy eligibility was defined as a confirmed hematocrit greater than 45% that is at least 3 percentage points higher than the hematocrit obtained at baseline or a confirmed hematocrit greater than 48%, whichever was lower. Secondary endpoints included the proportion of all randomized subjects who achieved the primary endpoint and who maintained their response 48 weeks after randomization, and the proportion of subjects achieving complete hematological remission at Week 32 with complete hematological remission defined as achieving hematocrit control, platelet count less than or equal to 400 X 10^9/L, and white blood cell count less than or equal to 10 X 10^9/L.

Results of the primary and secondary endpoints are presented in Table 16. A significantly larger proportion of patients on the Jakafi arm achieved a response for the primary endpoint compared to best available therapy at Week 32 and maintained their response 48 weeks after randomization. A significantly larger proportion of patients on the Jakafi arm compared to best available therapy also achieved complete hematological remission at Week 32.

Reference ID: 4165150

Table 16: Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in Study 3 (Intent to Treat)

	Jakafi (N=110)	**Best Available Therapy (N=112)**
Number (%) of Patients Achieving a Primary Response at Week 32	25 (23%)	1 (<1%)
95% CI of the response rate (%)	(15%, 32%)	(0%, 5%)
P-value	< 0.0001	
Number (%) of Patients Achieving a Durable Primary Response at Week 48	22 (20%)	1 (<1%)
95% CI of the response rate (%)	(13%, 29%)	(0%, 5%)
P-value	< 0.0001	
Number (%) of Patients Achieving Complete Hematological Remission at Week 32	26 (24%)	9 (8%)
95% CI of the response rate (%)	(16%, 33%)	(4%, 15%)
P-value	0.0016	

Primary Response defined as having achieved both the absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32 and a greater than or equal to 35% reduction from baseline in spleen volume at Week 32.

Additional analyses for Study 3 to assess durability of response were conducted at Week 80 only in the Jakafi arm. On this arm, 91 (83%) patients were still on treatment at the time of the Week 80 data cut-off. Of the 25 patients who achieved a primary response at Week 32, 19 (76% of the responders) maintained their response through Week 80, and of the 26 patients who achieved complete hematological remission at Week 32, 15 (58% of the responders) maintained their response through Week 80.

In an assessment of the individual components that make up the primary endpoint, there were 66 (60%) patients with hematocrit control on the Jakafi arm vs. 21 (19%) patients on best available therapy at Week 32; 51 (77% of hematocrit responders) patients on the Jakafi arm maintained hematocrit control through Week 80. There were 44 (40%) patients with spleen volume reduction from baseline greater than or equal to 35% on the Jakafi arm vs. 1 (<1%) patient on best available therapy at Week 32; 43 (98% of spleen volume reduction responders) patients on the Jakafi arm maintained spleen volume reduction through Week 80.

Reference ID: 4165150

16 HOW SUPPLIED/STORAGE AND HANDLING

Jakafi (ruxolitinib) Tablets are available as follows:

Jakafi Trade Presentations

NDC Number	Strength	Description	Tablets per Bottle
50881-005-60	5 mg	Round tablet with “INCY” on one side and “5” on the other	60
50881-010-60	10 mg	Round tablet with “INCY” on one side and “10” on the other	60
50881-015-60	15 mg	Oval tablet with “INCY” on one side and “15” on the other	60
50881-020-60	20 mg	Capsule shaped tablet with “INCY” on one side and “20” on the other	60
50881-025-60	25 mg	Oval tablet with “INCY” on one side and “25” on the other	60

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Discuss the following with patients prior to and during treatment with Jakafi:

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.

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.

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.

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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.

Lipid Elevations

Inform patients that Jakafi may increase blood cholesterol, and of the need to monitor blood cholesterol levels.

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.

Dialysis

Inform patients on dialysis that their dose should not be taken before dialysis but only following dialysis.

Lactation

Inform women not to breastfeed during treatment with Jakafi and for two weeks after the final dose.

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
Wilmington, DE 19803

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U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 8829013; 9079912
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Reference ID: 4165150