The starting dose of Jakafi is based on the patient’s baseline platelet count:

- If the platelet count is less than or equal to 200 × 10^9/L twice daily, 10 mg:
- If the platelet count is less than or equal to 100 × 10^9/L twice daily, 5 mg:
- If the platelet count is less than or equal to 50 × 10^9/L twice daily, 2.5 mg:

• Thrombocytopenia, Anemia and Neutropenia: Manage by dose reduction, or interruption, or transition, (5.1)• Monitor complete blood counts every 2 to 4 weeks until doses are stabilized,

The recommended starting dose of Jakafi is 10 mg given orally twice daily. Treatment interruption and restarting dosing:

- Treatment interruption and restarting dosing (5.1)• Hematologic Interactions (5.1)• Nonhematologic Adverse Reactions (5.2)• Clinical Pharmacology (5.3)• Dose Management after Restarting Treatment (5.4)• Hematologic Management Guidelines for Patients with Myelofibrosis (7.1)• Acute Graft-Versus-Host Disease (7.4)• Use in Specific Populations (8)• Laboratory Tests (10)• Uses in Special Populations (11)• Pregnancy (12)• Pediatric Use (13)• Animal Data (14)• Clinical Pharmacology (15)• Diabetes (16)• Impairment of Fertility (17)• Congenital Abnormalities and Reproduction Studies (18)• Carcinogenesis, Mutagenesis, Impairment of Fertility (19)• Clinical Trials (20)• Conditions of Approval (21)• Initial U.S. Approval: 2011

Dose Modifications for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 50 × 10^9/L to Less Than 100 × 10^9/L

- The starting dose of Jakafi is 10 mg given orally twice daily. After restarting Jakafi following treatment interruption, doses may be titrated, but the dose should not exceed 15 mg given orally twice daily. The starting dose of Jakafi may be reduced to 5 mg given orally twice daily in patients who are unable to tolerate Jakafi at a dose of 10 mg given orally twice daily.

Hematology Laboratory Tests

- Monitor complete blood counts every 2 to 4 weeks until doses are stabilized, and then as clinically indicated (see Warnings and Precautions [5.1]).

Clinically significant thrombocytopenia

- Hemoglobin greater than or equal to 12 g/dL OR platelet count 25 to less than 75 × 10^9/L OR ANC 10 to less than 20 × 10^9/L

- Patients who have received increased Jakafi dose greater than or equal to 10 mg given orally twice daily and who have demonstrated clinical improvement during the prior four weeks.

- If a patient is started on Jakafi as a result of a new diagnosis of acute graft-versus-host disease, the dose should be increased to 15 mg given orally twice daily after the initial dose of 10 mg given orally twice daily.

- The starting dose of Jakafi is based on the patient’s baseline platelet count:

- The starting dose of Jakafi is based on safety and efficacy:

- If the platelet count is less than or equal to 200 × 10^9/L twice daily, 10 mg:
- If the platelet count is less than or equal to 100 × 10^9/L twice daily, 5 mg:
- If the platelet count is less than or equal to 50 × 10^9/L twice daily, 2.5 mg:

- Hemoglobin less than or equal to 12 g/dL OR platelet count 25 to less than 75 × 10^9/L OR ANC 10 to less than 20 × 10^9/L

- Patients who have received increased Jakafi dose greater than or equal to 10 mg given orally twice daily and who have demonstrated clinical improvement during the prior four weeks.

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- If the platelet count is less than or equal to 100 × 10^9/L twice daily, 5 mg:
- If the platelet count is less than or equal to 50 × 10^9/L twice daily, 2.5 mg:

- Hemoglobin less than or equal to 12 g/dL OR platelet count 25 to less than 75 × 10^9/L OR ANC 10 to less than 20 × 10^9/L

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- If the platelet count is less than or equal to 50 × 10^9/L twice daily, 2.5 mg:

- Hemoglobin less than or equal to 12 g/dL OR platelet count 25 to less than 75 × 10^9/L OR ANC 10 to less than 20 × 10^9/L

- Patients who have received increased Jakafi dose greater than or equal to 10 mg given orally twice daily and who have demonstrated clinical improvement during the prior four weeks.

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- If the platelet count is less than or equal to 50 × 10^9/L twice daily, 2.5 mg:

- Hemoglobin less than or equal to 12 g/dL OR platelet count 25 to less than 75 × 10^9/L OR ANC 10 to less than 20 × 10^9/L

- Patients who have received increased Jakafi dose greater than or equal to 10 mg given orally twice daily and who have demonstrated clinical improvement during the prior four weeks.

- If a patient is started on Jakafi as a result of a new diagnosis of acute graft-versus-host disease, the dose should be increased to 15 mg given orally twice daily after the initial dose of 10 mg given orally twice daily.
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 for up to 2.5 weeks or less. In the placebo-controlled study, some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, dyspnea, hypotension, or multi-organ failure. In some of these cases, no clinical improvement was observed while restarting the dose of Jakafi, evaluating and treating any intercurrent illness and considering 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 any reason, patients should be monitored for clinical symptoms of myeloproliferative neoplasms until symptoms have reached baseline.

5.4 Non-Melanoma Skin Cancer

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

5.5 Lipid Elevation

In clinical trials, Jakafi was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these changes on cardiovascular risk is unknown. Consequently, patients not already receiving lipid-lowering therapy should have a baseline lipid profile. In clinical trials, lipid parameters increased by approximately 15% at 8 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of this labeling:

- Thrombocytopenia, Anemia, and Neutropenia [see Warnings and Precautions (5.2)]
- Risk of Infection [see Warnings and Precautions (5.2)]
- Gastrointestinal 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)]
- Myelodysplastic Syndrome

6.1 Clinical Trial 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 treatment 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 8.5 months. In the placebo-controlled study, patients continued to receive placebo for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 109 patients started treatment at 20 mg twice daily. In the placebo-controlled study, patients treated with Jakafi and placebo treated patients had a median duration of treatment with Jakafi of 10.9 months, and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10⁹/L), 65% and 25% of patients, respectively, achieved 15% or greater reduction in spleen volume. In the placebo-controlled study, patients treated with Jakafi and placebo treated patients had a median duration of treatment with Jakafi of 10.9 months, and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10⁹/L), 65% and 25% of patients, respectively, achieved 15% or greater reduction in spleen volume.

In a double-blind, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and neutropenia. Jakafi exposure during clinical trials was limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, receiving Jakafi for signs and symptoms of active tuberculosis, and manage promptly. Risk factors, including but not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis with an inadequate course of treatment, cannot be completely excluded.

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 due to the risk of active tuberculosis should be based on the overall risk–benefit determination. Although no drug interaction studies were conducted, drug interactions are possible with Jakafi due to its extensive metabolism.
7  DRUG  INTERACTIONS

Concomitant administration of Jakafi with fluconazole doses greater than 200 mg/day may be associated with a significant increase in P-gp inhibitory activity. Ketoconazole (a strong CYP3A4 inhibitor) increased ruxolitinib Cmax by 33% and AUC by 91%. Ketoconazole also prolonged ruxolitinib half-life from 3.7 hours to 6 hours [see Clinical Pharmacology (12.3) and Drug Interactions (7)].

Ruxolitinib and its M18 metabolite did not inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OATP2B1, and OCT1 transporters. However, ruxolitinib and its active metabolites increased by 1.3-, 1.5-, and 1.9-fold in subjects with mild, moderate, and severe renal impairment, respectively. The changes in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure relative to the removal of some active metabolites by dialysis could not be ruled out.

Food Effect

Following a single oral dose of ratibulinib, elimination was predominantly renally mediated with the unchanged drug accounting for less than 1% of the excreted total radioactivity. The pharmacokinetics of ruxolitinib were independent of food. The mean AUC and Cmax increased by 29% and 52% with food, respectively. Unlike placebo. A similar proportion of patients in the Jakafi and best available therapy arm had greater reduction of spleen volume as measured by MRI or CT from baseline to Week 24 in both studies compared to placebo in both studies.

10 OVERDOSAGE

There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been administered to humans without any reports of acute or delayed toxicity. Experience with overdose is limited. The effects of overdose are generally associated with increased myeloproliferation including leukemia, anemia, thrombocytosis, and peripheral blood abnormalities. Sepsis and multi-organ failure have been reported. Hemorrhage is not expected to enhance the elimination of Jakafi.

11  DESCRIPTION

Jakafi is a white to off-white, film-coated tablet containing 5 mg and 10 mg ruxolitinib phosphate. Each tablet contains the following inactive ingredients: lactose monohydrate, corn starch, magnesium stearate, polyvinyl alcohol, and methylcellulose.

12  CLINICAL PHARMACOLOGY

12.1  Mechanism of Action

Ruxolitinib inhibits cytokine-induced phosphorylation of STAT3 in whole blood from patients with MF and PV. Jakafi administration resulted in maximal inhibition of STAT3 phosphorylation within 4 hours. In a single-dose study, the maximum plasma AUC of ruxolitinib is approximately 8 times the clinical exposure at the maximum recommended dose of 25 mg twice daily.

12.2  Pharmacodynamics

Jakafi was associated with a significant increase in platelet counts and a decrease in spleen volume as measured by MRI or CT of 2381 cm3 (range 451 cm3 to 7765 cm3). In patients with MF and PV, Jakafi administration resulted in maximal inhibition of STAT3 phosphorylation within 4 hours. Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9.

12.3  Pharmacokinetics

Mean ruxolitinib maximal plasma concentration (Cmax) and AUC increased proportionally over a single-dose range of 5 mg to 200 mg. Mean ruxolitinib Cmax ranged from 205 nM to 7100 nM and ruxolitinib AUC ranged from 2.8 to 195 hours × μmol/L over a single dose range of 5 mg to 200 mg.

In a post- and randomized study in rats, ruxolitinib was administered orally to lactating rats at a dose level equivalent to 10 mg/kg/day and to rats at doses of 10 mg/kg/day. The doses of ruxolitinib were selected based on its therapeutic index and its maximum tolerated dose (4× the clinical exposure at the maximum recommended dose of 25 mg twice daily).

13  NONCLINICAL TOXICOLOGY

13.1  Carcinogenesis, Mutagenesis, Impairment of Fertility

Ruxolitinib was not mutagenic in in vitro tests using a variety of bacterial and mammalian cell systems. It was not genotoxic in in vivo tests using rat and mouse bone marrow micronucleus assay or in a bone marrow micronucleus assay in rats. In rats, ruxolitinib was administered to males prior to and throughout gestation and females prior to mating and up to and including the implantation day (day 7). Ruxolitinib had no effect on fertility and reproductive performance in males (0 mg/day) and females (10, 100, and 200 mg/day). In female rats, ruxolitinib dosages of greater than or equal to 10 mg/kg resulted in developmental toxicity and decreased fetal body weight at doses of 10 mg/kg/day and 200 mg/kg/day. In male rats, ruxolitinib resulted in a decreased litter size at 100 mg/kg/day and decreased body weight gain at all dose levels. Ruxolitinib administered at or above 100 mg/kg/day in male rats also resulted in decreased reproductive indices (increased number of males with testicular atrophy). In general, the major effect of ruxolitinib on fertility appeared to be a dose-related reduction in testicular weight in the male. No evidence of impaired fertility or congenital abnormalities was observed in offspring of male or female rats treated with ruxolitinib for 104 days at or above 100 mg/kg/day.

In a fertility study, ruxolitinib was administered to male rats prior to and throughout mating and during the lactation period of the female (10 mg/kg/day). There were no treatment-related alterations in fertility or in any of the fertility indices such as sexual behavior, sperm counts, or fertility indices. The fertility of male and female rats was not adversely affected by ruxolitinib.

14  CLINICAL STUDIES

The starting dose of Jakafi was based on platelet count. Patients with a platelet count between 150 and 200 × 10^9/L were started on Jakafi 15 mg twice daily and patients with platelet counts greater than 200 × 10^9/L were started on Jakafi 20 mg twice daily. Doses were then individualized based on tolerability and efficacy with maximum doses of 20 and 25 mg twice daily reached by 19% and 33% of patients, respectively. The median platelet count was 110 × 10^9/L and 10% of patients had platelet counts between 75 to less than 100 × 10^9/L. Doses of 15 mg were recommended for patients with platelet counts between 50 to less than 75 × 10^9/L.

Study 1 (NCT00285289) was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The median duration of prior therapy was 8 months and 10 patients withdrew consent. Fifty percent (50%) of patients had prior polycythemia vera and 50% prior essential thrombocythemia. Twenty-one percent (21%) of patients had 100% or greater reduction in spleen volume as measured by MRI or CT of 2395 cm3 (range 941 cm3 to 7765 cm3). In patients with MF, the median change in spleen volume was -56% (range 29% to 100%). In patients with PV, the median change in spleen volume was -60% (range 29% to 98%). Patients were dosed with Jakafi or matching placebo. The primary endpoint was the proportion of patients achieving greater than or equal to a 35% reduction in spleen volume as measured by MRI or CT of 2395 cm3 (range 941 cm3 to 7765 cm3).

Study 2 (NCT00288495) was an open-label, randomized study in 210 patients. Patients were randomized to receive Jakafi 10 mg twice daily or placebo immediately following the completion of the last dose of prior therapy and were stratified based on the investigator on a patient-by-patient basis. In the best available therapy arm, the medications included interferon, hydroxyurea, anagrelide, and antiplatelet agents. The median age of patients was 64 years (range 18 to 88 years) and 50% of patients had 100% or greater reduction in spleen volume as measured by MRI or CT of 2395 cm3 (range 941 cm3 to 7765 cm3). In patients with MF, the median change in spleen volume was -52% (range 29% to 100%). In patients with PV, the median change in spleen volume was -56% (range 29% to 100%). Patients were dosed with Jakafi or matching placebo. The primary endpoint was the proportion of patients achieving greater than or equal to a 35% reduction in spleen volume as measured by MRI or CT of 2395 cm3 (range 941 cm3 to 7765 cm3).

The dosage of 10 mg of Jakafi twice daily with 100 mg to 400 mg of fluconazole once daily [see Dosage and Administration (2.4) and Drug Interactions (7)] resulted in maximal inhibition of STAT3 phosphorylation with a median percent reduction in spleen volume as measured by MRI or CT of 2395 cm3 (range 941 cm3 to 7765 cm3). The median change in spleen volume was -52% (range 29% to 100%). In patients with PV, the median change in spleen volume was -56% (range 29% to 100%). Patients were dosed with Jakafi or matching placebo. The primary endpoint was the proportion of patients achieving greater than or equal to a 35% reduction in spleen volume as measured by MRI or CT of 2395 cm3 (range 941 cm3 to 7765 cm3).

Table 17: Percent of Patients with Myelofibrosis Achieving ≥35% or Greater Reduction in Spleen Volume from Baseline in Week 24 at Study 1 and Week 48 at Study 2 (TREAT 2 Futility Analysis)

<table>
<thead>
<tr>
<th>Week</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>68.8%</td>
<td>51.0%</td>
</tr>
<tr>
<td>48</td>
<td>83.6%</td>
<td>52.4%</td>
</tr>
</tbody>
</table>

Table 18: Improvement in Total Symptom Score (TSS) in Patients with Myelofibrosis

<table>
<thead>
<tr>
<th>TSS</th>
<th>Baseline</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>62.1%</td>
<td>51.0%</td>
</tr>
<tr>
<td>30</td>
<td>57.1%</td>
<td>46.2%</td>
</tr>
</tbody>
</table>

Figure 1 shows the percent change from baseline in spleen volume for each patient at Week 24 for patients with MF who did not complete 24 weeks of randomized treatment. Jakafi-N=146, placebo-N=107. Results from patients who did not complete 24 weeks of randomized treatment (N=16) were pooled with the missing baseline data to calculate the percent change. Figure 2 shows the percent change from baseline in TSS for each patient at Week 24 for patients who did not complete 24 weeks of randomized treatment (jakafi-N=16, placebo-N=16). Results from patients who did not complete 24 weeks of randomized treatment (N=18) were pooled with the missing baseline data to calculate the percent change.
Figure 2: Percent Change from Baseline to Total Symptom Score at Week 24 for Last Observation Carried Forward analysis. (a) All patients. (b) Patients who received 10 mg twice daily as the starting dose. (c) All patients. (d) An exploratory analysis of patients receiving Jakafi also showed improvement in fatigue-related symptom severity (i.e., duration, intensity, emotional, mental, physical, and pain and fatigue) and level of activity and energy associated with participation in work, family, and social activities.

**Table 19: Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in a 3 Intent-to-Treat**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Jakafi</th>
<th>Best Available Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Number (%)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Primary Response</td>
<td>25 (23.7%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hematological Remission at Week 32</td>
<td>25 (23.7%)</td>
<td>1.0 (1.0-1.0)</td>
</tr>
</tbody>
</table>

**What is Jakafi?**

Jakafi is a prescription medicine used to treat:
- adults with myelofibrosis
- adults with polycythemia vera (PV) who have already taken a medicine called hydroxyurea and it did not work well enough or has not been tolerated
- adults and children 12 years of age and older with acute graft-versus-host disease (GVHD) who have taken corticosteroids and they did not work well enough.

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

Before taking Jakafi, tell your healthcare provider about your medical conditions, including if you:
- have or had tuberculosis (TB), or have been in close contact with someone who has TB
- have or had liver problems or are on dialysis. If you are on dialysis, tell your healthcare provider prior to starting treatment with Jakafi.
- have high level of fat in your blood (high blood cholesterol or triglycerides)
- have had skin cancer in the past
- have any other medical conditions

Inform women not to breastfeed during treatment with Jakafi and for two 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. Jakafi may affect how other medicines work and 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.

What are the possible side effects of Jakafi?

Jakafi can cause serious side effects including:
- low blood cell counts:
  - low platelet counts (thrombocytopenia), low red blood cell counts (anemia), and low white blood cell counts (neutropenia)
- increased cholesterol levels.

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:
- fever
- aches
- a cough or cold
- a sore throat
- diarrhea
- vomiting
- abdominal pain
- feeling tired
- skin rashes, hives, or blisters

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:

- chills
- fever
- a sore throat
- feeling tired
- a skin rash

Skin cancers. Some people who take Jakafi have developed certain types of non-melanoma skin cancers. Tell your healthcare provider if you develop any of the following symptoms:

- changes in the moles or skin:
  - change in size, shape, or color
- skin lumps
- scaly patches
- areas of skin that crust over
- sores that do not heal

These are not all the possible side effects of Jakafi.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

Jakafi (ruxolitinib) Tablets are available as follows:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Number of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>60</td>
</tr>
<tr>
<td>10 mg</td>
<td>60</td>
</tr>
</tbody>
</table>

**Table 20: Day-28 Overall Response Rate for Patients with Steroid-Resistant Acute GVHD in Study 4**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Overall Response (%) (95% CI)</th>
<th>Complete Response (%) (95% CI)</th>
<th>Partial Response (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi (ruxolitinib)</td>
<td>79% (59%, 99%)</td>
<td>7% (3%, 13%)</td>
<td>72% (53%, 87%)</td>
</tr>
</tbody>
</table>

**Table 18: Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in a 3 Intent-to-Treat**

<table>
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<tr>
<th>Endpoint</th>
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<tr>
<td>Hematological Remission at Week 32</td>
<td>25 (23.7%)</td>
<td>1.0 (1.0-1.0)</td>
</tr>
</tbody>
</table>

**What are the ingredients in Jakafi?**

**Active ingredient:** ruxolitinib

**Inactive ingredients:** lactose monohydrate, magnesium stearate, cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, and crospovidone.

Manufactured for Incyte Corporation by Aquaforte Cut-off, Wiltse, Virginia 22669. Jakafi is a registered trademark of Incyte, Xyrem is also a registered trademark of Incyte.

For more information call 1-855-463-3643 or go to www.jakafi.com.

This product information has been approved by the U.S. Food and Drug Administration. Revised: January 2020.