Dose Modification Based on Insufficient Response for Patients with Myelofibrosis

1. Myelofibrosis

Jakafi is a kinase inhibitor indicated for treatment of:

- Myelofibrosis
- Polycythemia vera

2. Administration and Dosage

2.1 Starting Dose

For patients on 5 mg twice daily, decrease dose by 5 mg twice daily.

For patients on 5 mg once daily, decrease dose by 5 mg once daily.

3. Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors

If the response is insufficient and platelet and neutrophil counts are adequate, doses may be decreased more aggressively. It is important to monitor patients closely for a maximum of 5 mg twice daily, which should be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Dose reductions should be considered if the platelet counts decrease as outlined in Table 3.

4. Dose Modifications Guided for Hematologic Toxicity for Patients with Myelofibrosis

5.3 Symptom Exacerbation Following Interruption

6.1 Clinical Trials Experience in Myelofibrosis

6.2 Risk of Infection

6.1.3 Chronic Myeloproliferative Disorders

6.2.1 Myelofibrosis

7.7 Gastrointestinal Malignancies

8.7.1 Gastrointestinal Malignancies

9.2 Use in Elderly Patients

10.7 Renal Impairment

11.12 Mechanism of Action

11.12.1 JAK, aKey to Cancer Pathways

14.1  Myelofibrosis

14.1.1 Hematologic Malignancies

14.1.2 Clinical Safety

14.1.2.1 Myeloproliferative Disease

15.3 Indications for Clinical Trials

15.3.1 Myeloproliferative Disorders

15.4.1 Hematologic Malignancies

16.1  Mechanism of Action

16.2  Application

16.2.1 Myelofibrosis

16.2.2 Polycythemia Vera

17.1  Patient Counseling

17.1.1 Myelofibrosis

17.1.1.1 Hematologic Malignancies

18.2  Lactation

18.3  Pregnancy

18.4  Nursing Mothers

20.2  Treatment of Radiation-Induced Cataracts

21.1  Mechanism of Action

21.2  Clinical Safety

21.2.1 Myelofibrosis

21.3.1 Hematologic Malignancies

21.4.1 Clinical Safety

21.4.1.1 Hematologic Malignancies

22.2  Use in Elderly Patients

22.2.1 Myelofibrosis

22.2.2 Polycythemia Vera

22.2.3 Clinical Safety

22.2.3.1 Myeloproliferative Disease

22.2.4 Hematologic Malignancies

22.2.4.1 Clinical Safety

22.2.4.2 Hematologic Malignancies

23.1  Dosage Modifications for Concomitant Use with Strong CYP3A4 Inhibitors

23.1.1 Myelofibrosis

23.1.1.1 Hematologic Malignancies

23.2  Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors

23.2.1 Polycythemia Vera

23.2.1.1 Hematologic Malignancies

23.3  Hematologic Toxicity

23.3.1 Myelofibrosis

23.3.1.1 Hematologic Malignancies

23.4  Gastrointestinal Malignancies

23.4.1 Myelofibrosis

23.4.1.1 Hematologic Malignancies

23.5  Gastrointestinal Malignancies

23.5.1 Myelofibrosis

23.5.1.1 Hematologic Malignancies

23.6  Malignant Lymphoma

23.6.1 Myelofibrosis

23.6.1.1 Hematologic Malignancies
Peripheral blood counts should be monitored before and during treatment with Jakafi, and neutropenia should be managed with dose reduction or dose interruption.

5.1 Thrombocytopenia, Anemia and Neutropenia

Thrombocytopenia

Thrombocytopenia has been reported in patients receiving Jakafi. Observations reflect the efficacy of Jakafi in association with other supportive therapies and manage prophylactically.

Prior to initiating Jakafi, patients should be evaluated for thrombocytopenia risk factors, and those at high risk should be followed for infection. Risk factors include, but are not limited to, a recent history in a blood donor or countries with a high prevalence of thrombocytopenia, close contact with a person with active thrombocytopenia, and a history of active or latent tuberculosis which may be more likely to re-activate in the presence of immunosuppression.

For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the evaluation and 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. The incidence of PML at 1 year was 1%.

Hypersensitivity

Hypersensitivity (including anaphylaxis) has occurred with or without associated elevations in liver enzymes. In these cases, hepatic enzymes have returned to normal after discontinuation of treatment with Jakafi.

Tuberculosis

Tuberculosis infection has been reported in patients receiving Jakafi. Observations reflect the efficacy of Jakafi in association with other supportive therapies and manage prophylactically.

Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at high risk should be followed for infection. Risk factors include, but are not limited to, a recent history in a blood donor or countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis which may be more likely to re-activate in the presence of immunosuppression.

For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the evaluation and 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.

5.2 Other Hematologic and Lymphohematologic Effects

5.2.1 Neutropenia

Neutropenia

Neutropenia is a common adverse reaction associated with Jakafi treatment. Neutropenia is generally reversible with dose reduction or dose interruption. The median time to recovery of neutrophil count to greater than or equal to 1.4 x 10⁹/L was approximately 5 weeks. Neutropenia was observed in up to 30% of patients receiving Jakafi in the open-label, active-controlled study. Neutropenia was observed in up to 4% of patients receiving placebo in the placebo-controlled study.

5.2.2 Anemia

Anemia

Anemia is a common adverse reaction associated with Jakafi treatment. Anemia is generally reversible with dose reduction or dose interruption. The median time to recovery of hemoglobin to greater than or equal to 12 g/dL was approximately 6 weeks. Anemia was observed in up to 65% of patients receiving Jakafi in the open-label, active-controlled study. Anemia was observed in up to 9% of patients receiving placebo in the placebo-controlled study.

5.2.3 Thrombocytopenia

Thrombocytopenia

Thrombocytopenia is a common adverse reaction associated with Jakafi treatment. Thrombocytopenia is generally reversible with dose reduction or dose interruption. The median time to recovery of platelet count to greater than or equal to 50 x 10⁹/L was approximately 5 weeks. Thrombocytopenia was observed in up to 65% of patients receiving Jakafi in the open-label, active-controlled study. Thrombocytopenia was observed in up to 7% of patients receiving placebo in the placebo-controlled study.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience in Myelofibrosis

6.1.1 Dosage-Dependent Adverse Reactions

6.1.1.1 Anemia

Anemia

Jakafi (N=71)

Best Available Therapy (N=34)

All Grades

Grade 3

Grade 4

Best Available Therapy

Grade 3

Grade 4

All Grades

Grade 3

Grade 4

Anemia

72

6

0

58

5

0

Neutropenia

24

3

0

13

0

0

Thrombocytopenia

20

3

0

8

0

0

Febrile Neutropenia

2

0

0

1

0

0

Disseminated Intravascular Coagulation (DIC)

1

0

0

1

0

0

6.1.2 Other Clinical Trials Experience

6.2.1 Clinical Trial Experience in Polycythemia Vera

6.2.1.1 Dosage-Dependent Adverse Reactions

6.2.1.1.1 Anemia

Anemia

Jakafi (N=274)

Best Available Therapy (N=99)

All Grades

Grade 3

Grade 4

Best Available Therapy

Grade 3

Grade 4

All Grades

Grade 3

Grade 4

Anemia

70

5

0

47

0

0

6.2.2 Other Clinical Trials Experience

6.2.2.1 Adverse Events

Adverse Events

All Grades

Grade 3

Grade 4

All Grades

Grade 3

Grade 4

All Grades

Grade 3

Grade 4

All Grades

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All Grades
7. **DRUG INTERACTIONS**

Fluconazole

Concomitant administration of Jakafi with fluconazole doses greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of the CYP3A4 enzyme system and the small apparent volume of distribution of ruxolitinib. The drug interaction with fluconazole occurred in a clinical study in which patients were administered ruxolitinib at a dose of 25 mg twice daily for 7 days while concomitantly receiving fluconazole doses of 100 mg once daily. When ruxolitinib was co-administered with fluconazole, ruxolitinib AUC by approximately 100% to 300% following concomitant administration.

Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg/day.

**Drug Interactions**

**8. USE IN SPECIFIC POPULATIONS**

**Risk Summary**

When Jakafi was administered to adult or pediatric patients, neutralizing antibodies developed in some patients dosed with the maximum recommended dose of Jakafi based on safety and efficacy [Clinical Pharmacology (12.3)]. No dose adjustment in patients with renal impairment is necessary for doses up to 25 mg twice daily.

The background risk of major birth defects and miscarriage for the indicated populations is 2% to 4% and 15% to 20% of clinically recognized pregnancies. There are no studies with use of the Jaakafi in pregnant women. Use of Jakafi in pregnancy should be restricted to women to inform drug-associated risks.

**Data Analysis**

Data from studies Jakafi in adult patients with PV, MF and MF under treatment with Jakafi and in adult patients with acute GVHD who received monotherapy with Jakafi were chosen for analysis. Adverse events were evaluated for all patients who received at least one dose of Jakafi in the clinical studies. Laboratory abnormalities were evaluated in patients who received Jakafi for at least one post-baseline laboratory test. Patients with PV are the primary analysis population (total AUC 25 mg twice daily).

**6.2.1 Lactation Risk Summary**

The effects of Jakafi on breastfeeding infants are unknown. Current data are insufficient to determine whether Jakafi administered to mothers breast feeds in breastfed infants.

**6.4. Pediatric Use**

There are no available data on the safety and effectiveness of Jakafi in pediatric patients. The safety and effectiveness of Jakafi in pediatric patients was evaluated in a single-dose study (NCT01619104) in 36 patients aged 12 weeks to 18 years with PV or MF aged 12 years and older. Use of Jakafi in pediatric patients with PV or MF and Splenomegaly remained the recommended dose for children older than 15 years of age.

**8. ADVERSE REACTIONS**

**Duration of Use**

There is no known benefit for Jakafi in patients with PV who have achieved a complete hematologic response and are no longer dosing. In this population, Jakafi should be considered only as part of a multi-modality approach to chronic myeloid leukemia.

**Periodic Laboratory Evaluations**

**7. DOSAGE AND ADMINISTRATION**

**JAK-STAT signaling pathways play a role in regulating the development, proliferation, and localization of STATs to the nucleus leading to modulation of gene expression.**

**13. NONCLINICAL TOXICOLOGY**

**13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility**

Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or in a chromosome aberration assay in vitro in human fibroblasts. Ruxolitinib did not induce the Pig-BCP, OATP1B1, OATP1B3, OATP2, OCT1, OCT2, or OAT1 transport systems at clinically relevant concentrations. Ruxolitinib is not a substrate for the P-gp transporter.

**Table 13: Percent of Patients Achieving a 35% or Greater Reduction in Spleen Volume from Baseline in Spleen Volume at Week 24 in Study 1 and Week 6 in Study 2 (Study 2)**

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Week 24</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>1.05%</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

**Table 14: Safety and Efficacy in Studies 1 and 2 in Adult Patients with MF**

**Observation for Each Patient (Study 1)**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to response</td>
<td>3.6 months</td>
<td>3.3 months</td>
</tr>
<tr>
<td>Median time to response</td>
<td>4.8 months</td>
<td>4.2 months</td>
</tr>
</tbody>
</table>

**Table 15: Percent of Patients Receiving a Complete Hematologic Response (CHR) for Each Patient (Study 1)**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>13.0%</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

**Table 16: Percent of Patients Receiving a Complete Hematologic Response (CHR) for Each Patient (Study 2)**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>13.0%</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

**Table 17: Percent of Patients Achieving a 35% or Greater Reduction in Total Symptom Score from Baseline in Studies 1 and 2**

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Week 6</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>3.6%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

**Figure 2** shows the percent change from baseline in spleen volume for each patient at Week 12 in Study 1 and in Week 6 in Study 2 in patients with MF. The data from Study 2 were more consistent and more patients achieved a greater or reduction in spleen volume compared to Study 1. The median spleen volume in patients who did not complete 24 weeks of randomized treatment (Study 1-N=56, placebo-N=56) was similar at 50% or greater reduction in spleen volume compared to baseline at Week 6.
Best Available Therapy 58
of subjects achieving complete hematological remission at Week 32 with complete included the proportion of all randomized subjects who achieved the primary endpoint Week 32). Phlebotomy eligibility was defined as a confirmed hematocrit greater than reduction (a greater than or equal to 35% reduction from baseline in spleen volume at response defined as having achieved both hematocrit control (the absence of phlebotomy The primary endpoint was the proportion of subjects achieving a response at Week 32, with anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). 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 10 mg twice daily, and 17% less than 10 mg twice daily. Best available therapy (BFT) was selected by the investigator on a per-patient basis and included hydroxyurea (6%), interferon-α (3%), interferon-β (1%), and interferon-λ (0%). For 6 patients, no information was available regarding dosage. The median duration of response was 24 weeks, with additional salvage therapy or increase in steroids) was 173 days (95% CI 63, 24, 126). The median age of 57 years (range, 18-72 years), 47% were male, 92% were Caucasian, and 14% had a median spleen volume as measured by MRI or CT of 1272 cm³ (range 254 cm³ to 5431 cm³) and median platelet count was 203 × 10³/µL. The ORR results are presented in Table 20; Day-28 ORR was 100% for Grade 2 GVHD, 93% for Grade 3 GVHD, and 49% for Grade 4 GVHD. The median duration of response was 31 days (range 1-350 days). A median of 2.2 years of follow-up was available for patients remaining on study in the intent-to-treat population with a median follow-up of 2.2 years (range 0.2-5.1 years). Patients who discontinued treatment included 97 patients who achieved durable complete hematological remission at Week 32 with complete hematological remission at Week 32, 15 (7.7%) of whom had a confirmed hematocrit greater than 35% reduction from baseline in spleen volume at Week 32. The ORR in patients with polycythemia vera achieving the primary and secondary endpoints is presented in Table 19. Results of the primary and secondary endpoints are presented in Table 18 and a significantly larger proportion of patients on the Jakafi arm achieved a response for the primary endpoint defined as best available therapy at Week 32 and maintained their response 48 weeks after randomization. A significantly larger proportion of patients on the Jakafi arm continued to be best available therapy also achieved complete hematological remission at Week 32. Table 19: Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in Study 3 (Intent to Treat)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Jakafi (N=191)</th>
<th>Best Available Therapy (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>90 (72, 97)</td>
<td>48 (39, 58)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
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</table>

Table 20: Day-28 Overall Response Rate for Patients with Sterile-Refractory Acute GVHD in Study 4

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Jakafi Therapy (N=112)</th>
<th>Best Available Therapy (N=104)</th>
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</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>81 (69, 88)</td>
<td>42 (27, 55)</td>
</tr>
<tr>
<td>P-value</td>
<td>2.3 × 10⁻⁶</td>
<td></td>
</tr>
</tbody>
</table>

Table 21:  Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in Study 3 (Intent to Treat)

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Table 22: Day-28 Overall Response Rate for Patients with Sterile-Refractory Acute GVHD in Study 4

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Table 23:  Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in Study 3 (Intent to Treat)

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Table 24: Day-28 Overall Response Rate for Patients with Sterile-Refractory Acute GVHD in Study 4

<table>
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<tbody>
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<tr>
<td>P-value</td>
<td>2.3 × 10⁻⁶</td>
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</table>

Table 25:  Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in Study 3 (Intent to Treat)

<table>
<thead>
<tr>
<th>Endpoint</th>
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<th>Best Available Therapy (N=191)</th>
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<tr>
<td>P-value</td>
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<td></td>
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</table>

Table 26: Day-28 Overall Response Rate for Patients with Sterile-Refractory Acute GVHD in Study 4

<table>
<thead>
<tr>
<th>Endpoint</th>
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