Guide for adding **JAKAFI XR™ (ruxolitinib)** extended-release tablets as a treatment in an EHR ("Guide")

Overview

This Electronic Health Record (EHR) build is an educational resource designed to support the safe use of ruxolitinib extended-release tablets post-prescription. This Guide is not designed or intended for use prior to a healthcare provider's (HCP's) prescription decision about whether ruxolitinib extended-release tablets may be appropriate for an individual patient and is not intended to influence HCP treatment decisions. Prescribers are responsible for making individualized prescribing decisions for their patients and should refer to the United States Prescribing Information (USPI) for the Food and Drug Administration (FDA)-approved indications and related information on the safe use of ruxolitinib extended-release tablets. This resource provides the information listed below, including relevant safety and dosing information from the USPI for ruxolitinib extended-release tablets.

1. Clinical Overview
2. EHR Specifications
3. Clinical Protocol Breakdown

Instructions and Limitations

This Guide is intended to provide guidance for use with the EHR system used by the HCP for the FDA-approved indications for ruxolitinib extended-release tablets only. This Guide will not work for other conditions or therapeutic-related areas.

- The HCP is responsible for implementation, testing, and monitoring of the instructions to ensure proper usage in the individual EHR system. The HCP has sole and complete responsibility for ensuring the accuracy of the EHR system. The HCP must determine the final elements to include in line with his or her organization's expectations, goals, and EHR governing principles
- The HCP is responsible for performing his or her own clinical review of these instructions and any other materials provided by Incyte, including the full Prescribing Information
- Capabilities, functionality, and set-up (customization) of each individual EHR system will vary. Incyte shall not be responsible for customizing or revising the implementation information it provides to any HCP. These materials have not been reviewed or endorsed by the EHR system used ("EHR Company"). Incyte has no affiliation or relationship with the EHR Company regarding these materials
- Incyte shall have no responsibility or liability whatsoever for HCP treatment decisions. This Guide provides information from the USPI for ruxolitinib extended-release tablets only and does not provide clinical advice or direction on how or whether HCPs should treat individual patients with ruxolitinib extended-release tablets. This Guide for ruxolitinib extended-release tablets is designed and intended to be used post-prescription only for the FDA-approved indications
- This Guide is not meant to be utilized for meeting meaningful use and/or other quality/accreditation requirements

1 - Clinical Overview

INDICATIONS AND USAGE

JAKAFI®/JAKAFI XR™ (ruxolitinib) is for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.

JAKAFI®/JAKAFI XR™ is for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

JAKAFI®/JAKAFI XR™ is for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older.

JAKAFI®/JAKAFI XR™ is for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Thrombocytopenia, Anemia and Neutropenia

• JAKAFI®/JAKAFI XR™ (ruxolitinib) can cause dose-related effects of thrombocytopenia, anemia and neutropenia. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
• Manage thrombocytopenia by reducing the dose or temporarily interrupting JAKAFI/JAKAFI XR. Platelet transfusions may be necessary.
• Patients developing anemia may require blood transfusions and/or dose modifications of JAKAFI/JAKAFI XR.
• Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding JAKAFI/JAKAFI XR until recovery.

Risk of Infection

Tuberculosis

• Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting JAKAFI/JAKAFI XR until active serious infections have resolved. Observe patients receiving JAKAFI/JAKAFI XR for signs and symptoms of infection and manage promptly.
• Tuberculosis (TB) infection with JAKAFI/JAKAFI XR has been reported. Observe patients taking JAKAFI/JAKAFI XR for signs and symptoms of active TB and manage promptly. Prior to initiating, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting in patients with evidence of active or latent TB. Continuation during treatment of active TB should be based on the overall risk-benefit determination.

Progressive Multifocal Leukoencephalopathy

• Progressive multifocal leukoencephalopathy (PML) has occurred with JAKAFI/JAKAFI XR treatment. If PML is suspected, stop JAKAFI/JAKAFI XR and evaluate.

Herpes Zoster and Herpes Simplex

• Herpes zoster infection, reactivation and/or dissemination has been reported in patients receiving JAKAFI/JAKAFI XR. Advise patients about early signs and symptoms of herpes zoster and seek treatment. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment.

Hepatitis B

• Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections.

Symptom Exacerbation Following Interruption or Discontinuation of Treatment

• When discontinuing JAK-Inhibitors, including JAKAFI/JAKAFI XR, myeloproliferative neoplasm-related signs and symptoms may flare. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, disseminated intravascular coagulation (DIC), or multi-organ failure. If any of these occur after discontinuation or while tapering JAKAFI/JAKAFI XR, evaluate and treat any intercurrent illness and consider restarting or increasing the dose. Instruct patients not to interrupt or discontinue JAKAFI/JAKAFI XR without consulting their

physician. When discontinuing or interrupting JAKAFI/JAKAFI XR for reasons other than life-threatening toxicities, consider gradual tapering rather than abrupt discontinuation.

Non-Melanoma Skin Cancer (NMSC)

• NMSC including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.

Lipid Elevations

• Treatment with JAKAFI/JAKAFI XR has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiation.

Major Adverse Cardiovascular Events (MACE)

• Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers), in patients with rheumatoid arthritis, a condition for which JAKAFI/JAKAFI XR is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis

• Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers), in patients with rheumatoid arthritis, a condition for which JAKAFI/JAKAFI XR is not indicated. In patients with myelofibrosis (MF) and polycythemia vera (PV), the rates of thromboembolic events were similar in JAKAFI/JAKAFI XR and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Secondary Malignancies

• Another JAK-inhibitor has increased the risk of lymphoma and other malignancies, excluding NMSC (compared to those treated with TNF blockers), in patients with rheumatoid arthritis, a condition for which JAKAFI/JAKAFI XR is not indicated. Patients who are current or past smokers are at additional increased risk.

Adverse Reactions

• In myelofibrosis, the most common hematologic adverse reactions (incidence >20%) were thrombocytopenia and anemia. The most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache and diarrhea

• In polycythemia vera, the most common hematologic adverse reactions (incidence >20%) were thrombocytopenia and anemia. The most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache and diarrhea.

• In acute graft-versus-host disease, the most common hematologic adverse reactions (incidence >50%) were anemia, thrombocytopenia and neutropenia. The most common nonhematologic adverse reactions (incidence >50%) were infections (pathogen not specified) and edema.

• In chronic graft-versus-host disease, the most common hematologic adverse reactions (incidence >35%) were anemia and thrombocytopenia. The most common nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and viral infections.

Drug Interactions

• Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.

Pregnancy

• Use during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking JAKAFI/JAKAFI XR should not breastfeed during treatment and for 2 weeks after the final dose.

Please see Full Prescribing Information for JAKAFI/JAKAFI XR.

DOSAGE AND ADMINISTRATION

Monitoring to Assess Safety

Prior to JAKAFI XR treatment:

- Perform a complete blood count (CBC). Please see Warnings and Precautions (5.1) in the Prescribing Information for more recommendations
- Inquire about past infections, including tuberculosis, herpes simplex, herpes zoster, and hepatitis B. Please see Warnings and Precautions (5.2) in the Prescribing Information for more recommendations

During treatment with JAKAFI XR:

- Perform a CBC every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Please see Warnings and Precautions (5.1) in the Prescribing Information for more recommendations
- Assess lipid parameters approximately 8 to 12 weeks following initiation of JAKAFI XR therapy. Please see Warnings and Precautions (5.5) in the Prescribing Information for more recommendations

Recommended Dosage for Myelofibrosis

The recommended starting dose of JAKAFI XR is based on platelet count (Table 1). Doses may be titrated based on safety and efficacy.

Table 1: JAKAFI XR Starting Doses for Myelofibrosis

Platelet Count	JAKAFI XR Starting Dose
Greater than 200×10^9/L	44 mg orally once daily
100×10^9/L to 200×10^9/L	33 mg orally once daily
50×10^9/L to less than 100×10^9/L	11 mg orally once daily

Recommended Dosage for Polycythemia Vera

The recommended starting dose of JAKAFI XR is 22 mg orally once daily.
Doses may be titrated based on safety and efficacy.

Recommended Dosage for Acute Graft-Versus-Host Disease

The recommended starting dose of JAKAFI XR is 11 mg given orally once daily. Consider increasing the dose to 22 mg once daily after at least 3 days of treatment if the absolute neutrophil count (ANC) and platelet counts are not decreased by 50% or more relative to the first day of dosing with JAKAFI XR.

Recommended Dosage for Chronic Graft-Versus-Host Disease

The recommended starting dose of JAKAFI XR is 22 mg given orally once daily.

Dosage Form and Strengths

JAKAFI XR:

11 mg extended-release tablets - round and light pink with “I” on one side and “11” on the other.

22 mg extended-release tablets - round and light yellow with “I” on one side and “22” on the other.

33 mg extended-release tablets - round and pink with “I” on one side and “33” on the other.

44 mg extended-release tablets - round and grey with “I” on one side and “44” on the other.

55 mg extended-release tablets - round and yellow with “I” on one side and “55” on the other.

Please see Full Prescribing Information for JAKAFI/JAKAFI XR.

You may report side effects to the US Food and Drug Administration by visiting https://www.fda.gov/medwatch or calling 1-800-FDA-1088. You may also report side effects to Incyte at 1-855-4-MEDINFO (855-463-3463).

2 - EHR Specifications

Agnostic Order Set Guide for **JAKAFI XR™ (ruxolitinib) extended-release tablets**

This Guide can be used to create a new or update an existing Order Set to include **JAKAFI XR™ (ruxolitinib)** extended-release tablets. JAKAFI XR™ (ruxolitinib) extended-release tablets are indicated for treatment of:

- Intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.
- Polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.
- Steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older.
- Chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

Refer to the **JAKAFI XR™ (ruxolitinib)** extended-release tablets full Prescribing Information as needed.

Consult EHR-specific User Guides to create a new Order Set or modify an existing Order Set.

1. Navigate to the Order Set section in your EHR system.
2. Perform designated steps to create a new or modify an existing Order Set.
    - Consult your EHR administrator if needed.

JAKAFI XR™ (ruxolitinib) extended-release tablets**:**

NDC(s):

NDC Number	Strength	Description	Tablets per Bottle
50881-011-08	11 mg	Round light pink tablet with “I” on one side and “11” on the other	30
50881-022-08	22 mg	Round light yellow tablet with “I” on one side and “22” on the other	30
50881-033-08	33 mg	Round pink tablet with “I” on one side and “33” on the other	30
50881-044-08	44 mg	Round grey tablet with “I” on one side and “44” on the other	30
50881-055-08	55 mg	Round yellow tablet with “I” on one side and “55” on the other	30

Store JAKAFI XR at 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].
Dispense in a tight container. Protect from light.

Packaging: Supplied in bottles containing 30 tablets

Strength(s): 11 mg • 22 mg • 33 mg • 44 mg • 55 mg

Dose: JAKAFI XR™ (ruxolitinib) extended-release tablets are for oral administration. Each tablet contains 11 mg, 22 mg, 33 mg, 44 mg, or 55 mg of ruxolitinib free base equivalent to 14.5 mg, 29 mg, 43.6 mg, 58.1 mg, or 72.6 mg of ruxolitinib phosphate, respectively.

3 - Clinical Protocol Breakdown

Protocol Name: Intermediate or high-risk myelofibrosis – JAKAFI XR™ (ruxolitinib) extended-release tablets
Disease Group: Myelofibrosis
Description: JAKAFI XR is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF in adults.

Protocol Name: Polycythemia Vera – JAKAFI XR™ (ruxolitinib) extended-release tablets
Disease Group: Polycythemia Vera
Description: JAKAFI XR is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

Protocol Name: Acute graft-versus-host disease – JAKAFI XR™ (ruxolitinib) extended-release tablets
Disease Group: Acute Graft-Versus-Host Disease
Description: JAKAFI XR is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older.

Protocol Name: Chronic graft-versus-host disease – JAKAFI XR™ (ruxolitinib) extended-release tablets
Disease Group: Chronic Graft-Versus-Host Disease
Description: JAKAFI XR is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

Treatment Plan Summary

Treatment Conditions

Physician Communication:

Thrombocytopenia, Anemia and Neutropenia
Inform patients that JAKAFI XR is associated with thrombocytopenia, anemia and neutropenia, and of the need to monitor CBC 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 (PML) and advise patients to seek the advice of a clinician if such symptoms are observed.
Symptom Exacerbation Following Interruption or Discontinuation of Treatment with JAKAFI XR
Inform patients that after discontinuation of treatment, signs and symptoms from myeloproliferative neoplasms may flare. Instruct patients not to interrupt or discontinue JAKAFI XR therapy without consulting their HCP.
Non-Melanoma Skin Cancer (NMSC)
Inform patients that JAKAFI XR may increase their risk of certain NMSCs. Advise patients to inform their HCP 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 XR may increase blood cholesterol, and of the need to monitor blood cholesterol levels.
Major Adverse Cardiovascular Events (MACE)
Advise patients that events of MACE including myocardial infarction, stroke, and cardiovascular death, have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which JAKAFI XR is not indicated. Advise patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis

Advise patients that events of deep vein thrombosis (DVT) or pulmonary embolism (PE) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which JAKAFI XR is not indicated. Advise patients to tell their HCP if they develop any signs or symptoms of a DVT or PE.

Secondary Malignancies

Advise patients, especially current or past smokers and patients with a known secondary malignancy (other than a successfully treated NMSC), that lymphoma and other malignancies (excluding NMSC) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which JAKAFI XR is not indicated.

Drug-Drug Interactions

Advise patients to inform their HCPs 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 XR and for 2 weeks after the final dose.

Compliance

Advise patients to continue taking JAKAFI XR 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 XR without first consulting their physician. Patients should be aware that after discontinuation of treatment, signs and symptoms from myeloproliferative neoplasms are expected to return.

Pre-Labs (category):

Physician Communication Order:

Monitoring to Assess Safety

Prior to JAKAFI XR treatment:

- Perform a complete blood count (CBC). Please see Warnings and Precautions (5.1) in the Prescribing Information for more recommendations
- Inquire about past infections, including tuberculosis, herpes simplex, herpes zoster, and hepatitis B. Please see Warnings and Precautions (5.2) in the Prescribing Information for more recommendations

During treatment with JAKAFI XR:

- Perform a CBC every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Please see Warnings and Precautions (5.1) in the Prescribing Information for more recommendations
- Assess lipid parameters approximately 8 to 12 weeks following initiation of JAKAFI XR therapy. Please see Warnings and Precautions (5.5) in the Prescribing Information for more recommendations

Medications (category):

Nursing Communication:

Recommended Dose

Recommended Dosage for Myelofibrosis

The recommended starting dose of JAKAFI XR is based on platelet count (Table 1). Doses may be titrated based on safety and efficacy.

Table 1: JAKAFI XR Starting Doses for Myelofibrosis

Platelet Count	JAKAFI XR Starting Dose
Greater than 200 × 10^9/L	44 mg orally once daily
100 × 10^9/L to 200 × 10^9/L	33 mg orally once daily
50 × 10^9/L to less than 100 × 10^9/L	11 mg orally once daily

JAKAFI XR

JAKAFI XR is dosed orally and can be administered with or without food.

Swallow JAKAFI XR tablets whole. Do not split, chew, or crush.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

When discontinuing JAKAFI XR therapy for reasons other than potentially life-threatening toxicities, gradually taper the dose of JAKAFI XR (eg, by 11 mg once daily each week for JAKAFI XR).

Recommended Dosage for Polycythemia Vera

The recommended starting dose of JAKAFI XR is 22 mg orally once daily.
Doses may be titrated based on safety and efficacy.

Recommended Dosage for Acute Graft-Versus-Host Disease

The recommended starting dose of JAKAFI XR is 11 mg given orally once daily. Consider increasing the dose to 22 mg once daily after at least 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with JAKAFI XR.

Recommended Dosage for Chronic Graft-Versus-Host Disease

The recommended starting dose of JAKAFI XR is 22 mg given orally once daily.

Physician Communication:

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

Dose Reductions

JAKAFI XR dose reductions should be considered if the platelet counts decrease as outlined in Table 2, with the goal of avoiding dose interruptions for thrombocytopenia.

Table 2: Myelofibrosis: JAKAFI XR Dosing Recommendations for Thrombocytopenia for Patients Starting Treatment With a Platelet Count of 100 × 10^9/L or Greater

	Dose at Time of Platelet Decline				
	55 mg Once Daily	44 mg Once Daily	33 mg Once Daily	22 mg Once Daily	11 mg Once Daily
Platelet Count	New Dose	New Dose	New Dose	New Dose	New Dose
100 to less than 125 × 10^9/L	44 mg once daily	33 mg once daily	No change	No change	No change
75 to less than 100 × 10^9/L	22 mg once daily	22 mg once daily	22 mg once daily	No change	No change

	Dose at Time of Platelet Decline				
50 to less than 75 × 10^9/L	11 mg once daily	11 mg once daily	11 mg once daily	11 mg once daily	No change
Less than 50 × 10^9/L	Hold	Hold	Hold	Hold	Hold

Treatment Interruption and Restarting Dosing

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

After recovery of platelet counts above 50 × 10^9/L and ANC above 0.75 × 10^9/L, dosing may be restarted. When restarting JAKAFI XR, begin with a dose that is at least 11 mg once daily below the dose at interruption. The maximum allowable dose that may be used in restarting JAKAFI XR after a previous interruption is outlined in Table 3 for thrombocytopenia and in Table 4 for neutropenia.

Table 3: Myelofibrosis: Maximum Restarting Doses for JAKAFI XR After Safety Interruption for Thrombocytopenia for Patients Starting Treatment With a Platelet Count of 100 × 10^9/L or Greater

Current Platelet Count	Maximum Dose When Restarting JAKAFI XR Treatment
Greater than or equal to 125 × 10^9/L	44 mg once daily
100 to less than 125 × 10^9/L	33 mg once daily
75 to less than 100 × 10^9/L	22 mg once daily for at least 2 weeks; if stable, may increase to 33 mg once daily
50 to less than 75 × 10^9/L	11 mg once daily for at least 2 weeks; if stable, may increase to 22 mg once daily
Less than 50 × 10^9/L	Continue hold

Table 4: Myelofibrosis: Maximum Restarting Doses for JAKAFI XR After Safety Interruption for Neutropenia (ANC < 0.5 × 10^9/L)

Current Neutrophil Count	Maximum Dose When Restarting JAKAFI XR Treatment
ANC ≥ 0.75 × 10^9/L	For patients on 11 mg once daily prior to the first interruption, restart at 11 mg once daily. Discontinue for a second interruption

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

If the response is insufficient and platelet and neutrophil counts are adequate, JAKAFI XR doses may be increased in 11 mg once daily increments to a maximum of 55 mg once 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 × 10^9/L at 4 weeks and platelet count never below 100 × 10^9/L;
c. ANC levels greater than 0.75 × 10^9/L.

Discontinue JAKAFI XR if there is no spleen size reduction or symptom improvement after 6 months of therapy.

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

This section applies only to patients with platelet counts of 50 × 10^9/L to less than 100 × 10^9/L prior to any treatment with JAKAFI XR. See dose modifications in Section 2.2 of the Prescribing Information *(Dose Modification Guidelines for Hematologic Toxicity for Patients With Myelofibrosis Starting Treatment With a Platelet Count of 100 × 10^9/L or Greater)* for hematological toxicity in patients whose platelet counts were 100 × 10^9/L or more prior to starting treatment with JAKAFI XR.

Dose Reductions

Reduce the dose of JAKAFI XR for platelet counts less than 35 × 10^9/L as described in Table 5.

Table 5: Myelofibrosis: Dosing Modifications for Thrombocytopenia for Patients With Starting Platelet Count of 50 × 10^9/L to Less Than 100 × 10^9/L

Platelet Count	**JAKAFI XR Dosing Recommendations**
25 × 10^9/L to less than 35 × 10^9/L AND the platelet count decline is 20% or greater during the prior 4 weeks	• Reduce dose by 11 mg once daily. • For patients on 11 mg once daily, interrupt dosing.
25 × 10^9/L to less than 35 × 10^9/L AND the platelet count decline is less than 20% during the prior 4 weeks	• Reduce dose by 11 mg once daily. • For patients on 11 mg once daily, interrupt dosing.
Less than 25 × 10^9/L	Interrupt dosing.

Treatment Interruption and Restarting Dosing

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

After recovery of platelet counts above 35 × 10^9/L and ANC above 0.75 × 10^9/L, dosing may be restarted. Restart dosing at the higher dose of JAKAFI XR 11 mg once daily, below the largest dose in the week prior to the treatment interruption. For patients on JAKAFI XR 11 mg once daily prior to the first interruption, continue JAKAFI XR 11 mg once daily. Discontinue JAKAFI XR for a second interruption.

Dose Modifications Based on Insufficient Response for Patients With Myelofibrosis and Starting Platelet Count of 50 × 10^9/L to Less Than 100 × 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 2.2 of the Prescribing Information *(see Dose Modification Based on Insufficient Response for Patients With Myelofibrosis Starting Treatment With a Platelet Count of 100 × 10^9/L or Greater)*, doses may be increased. For patients on JAKAFI XR 11 mg once daily, dose may be increased to a maximum of 22 mg once daily if:

a. The platelet count has remained at least 40 × 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 1×10^9/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 for whom the potential benefits outweigh the potential risks. Discontinue JAKAFI XR if there is no spleen size reduction or symptom improvement after 6 months of therapy.

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 XR at a lower dose.

Dose Modification Guidelines for Patients With Polycythemia Vera

Dose Reductions

Dose reductions should be considered for hemoglobin and platelet count decreases as described in Table 6.

Table 6: Polycythemia Vera: Dose Reductions

Hemoglobin and/or Platelet Count	JAKAFI XR Dosing Recommendations
Hemoglobin 10 to less than 12 g/dL AND platelet count 75 to less than 100 × 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 × 10^9/L	• Reduce dose by 11 mg once daily. • For patients on 11 mg once daily, interrupt dosing.
Hemoglobin less than 8 g/dL OR platelet count less than 50 × 10^9/L	Interrupt dosing.

Treatment Interruption and Restarting Dosing

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

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

Table 7 illustrates the dose that may be used in restarting JAKAFI XR after a previous interruption.

Table 7: Polycythemia Vera: Restarting Doses for JAKAFI XR 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	JAKAFI XR Maximum Restarting Dose
Hemoglobin less than 8 g/dL OR platelet count less than 50 × 10^9/L OR ANC less than 1 × 10^9/L	Continue hold

Hemoglobin, Platelet Count, or ANC	JAKAFI XR Maximum Restarting Dose
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 × 10^9/L OR ANC 1 to less than 1.5 × 10^9/L	11 mg once daily* or no more than 11 mg once 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 × 10^9/L OR ANC 1.5 to less than 2 × 10^9/L	22 mg once daily* or no more than 11 mg once 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 × 10^9/L OR ANC greater than or equal to 2 × 10^9/L	33 mg once daily* or no more than 11 mg once daily less than the dose which resulted in dose interruption

*Continue JAKAFI XR treatment for at least 2 weeks; if stable, may increase dose by 11 mg once daily.

JAKAFI XR

Patients who had required dose interruption while receiving a dose of 11 mg once daily may restart JAKAFI XR at a dose of 11 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 × 10^9/L, and ANC is greater than or equal to 1.5 × 10^9/L.

Dose Management After Restarting Treatment

After restarting JAKAFI XR following treatment interruption, doses may be titrated, but the maximum total daily dose should not exceed 11 mg once daily 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 XR would not be limited.

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:

Increase JAKAFI XR dose in 11 mg once daily increments to a maximum of 55 mg once 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:

1. Inadequate efficacy as demonstrated by 1 or more of the following:
    a. Continued need for phlebotomy
    b. White blood cell (WBC) count 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 × 10^9/L
3. Hemoglobin greater than or equal to 12 g/dL
4. ANC greater than or equal to 1.5 × 10^9/L

Recommended Dosage for Acute Graft-Versus-Host Disease

<u>JAKAFI XR</u>

The recommended starting dose of JAKAFI XR is 11 mg given orally once daily. Consider increasing the dose to 22 mg once daily after at least 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with JAKAFI XR.

<u>Treatment Completion</u>

Consider tapering JAKAFI XR after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper JAKAFI XR by one dose level approximately every 8 weeks using the dose levels shown in Table 8. If aGVHD signs or symptoms recur during or after the taper of JAKAFI XR, consider retreatment.

Table 8: Reduced Dose Levels for Patients With aGVHD or cGVHD

Dose Level	Recommended JAKAFI XR Dose
Maximum dose	22 mg once daily
Reduced dose level -1	11 mg once daily
Reduced dose level -2	Do not use JAKAFI XR

Dose Modification Guidelines for Patients With aGVHD

Monitor CBC, including platelet count and ANC, and bilirubin prior to initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as indicated clinically.

Modify the dose of JAKAFI XR for adverse reactions as described in Table 9. See Table 8 for the recommended dose when a dose reduction is needed.

Table 9: Dose Modifications for Adverse Reactions in Patients With aGVHD

Laboratory Parameter	Dosing Recommendations
Clinically significant thrombocytopenia after supportive measures	Reduce dose by 1 dose level. When platelets recover to previous values, dosing may return to prior dose level.
ANC less than 1×10^9/L considered related to JAKAFI XR	Hold JAKAFI XR up to 14 days; resume at 1 dose level lower upon recovery.[†]
Total bilirubin elevation, no liver GVHD	3.0-5.0 × ULN: Continue JAKAFI XR at 1 dose level lower until recovery.[†] > 5.0-10.0 × ULN: Hold JAKAFI XR for up to 14 days until bilirubin ≤ 1.5 × ULN; resume at current dose upon recovery. Total bilirubin > 10.0 × ULN: Hold JAKAFI XR for up to 14 days until bilirubin ≤ 1.5 × ULN; resume at 1 dose level lower upon recovery.[†]
Total bilirubin elevation, liver GVHD	> 3.0 × ULN: Continue JAKAFI XR at 1 dose level lower until recovery.[†]

[†]See Table 8 for reduced dose levels.

Dose Modification Guidelines for Patients With cGVHD

Monitor CBC, including platelet count and ANC, and bilirubin prior to initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as indicated clinically.

Modify the dose of JAKAFI XR for adverse reactions as described in Table 10. See Table 8 for the recommended dose when a dose reduction is needed.

Table 10: Dose Modifications for Adverse Reactions in Patients With cGVHD

Parameter	Dosing Recommendations
Platelet count less than 20×10^9/L	Reduce JAKAFI XR by 1 dose level.‡ If resolved within 7 days, dosing may return to initial dose level. If not resolved within 7 days, then maintain at 1 dose level lower.
ANC less than 0.75×10^9/L considered related to JAKAFI/JAKAFI XR	Reduce JAKAFI XR by 1 dose level‡; resume at initial dose level upon recovery.
ANC less than 0.5×10^9/L considered related to JAKAFI/JAKAFI XR	Hold JAKAFI XR for up to 14 days; resume at 1 dose level‡ lower upon recovery. May resume initial dose level when ANC greater than 1.0×10^9/L.
Total bilirubin: 3.0-5.0 × ULN	Continue JAKAFI XR at 1 dose level lower‡ until recovery. If resolved within 14 days, then increase by 1 dose level. If not resolved within 14 days, then maintain the reduced dose level.
Total bilirubin: > 5.0-10.0 × ULN	Hold JAKAFI XR for up to 14 days until resolved; resume at current dose upon recovery. If not resolved within 14 days, then resume at 1 dose level lower‡ upon recovery.
Total bilirubin: > 10.0 × ULN	Hold JAKAFI XR for up to 14 days until resolved; resume at 1 dose level lower‡ upon recovery. If not resolved within 14 days, discontinue.
Other Adverse Reactions: Grade 3	Continue JAKAFI XR at 1 dose level lower‡ until recovery.
Other Adverse Reactions: Grade 4	Discontinue JAKAFI XR.

‡See Table 8 for reduced dose levels.

Dose Modifications for Concomitant Use With Strong CYP3A4 Inhibitors or Fluconazole

Modify the JAKAFI XR dosage when coadministered with strong CYP3A4 inhibitors or doses of less than or equal to 200 mg of fluconazole *[see Drug Interactions (7)]*, according to Table 11. Avoid concomitant use of JAKAFI XR with fluconazole doses of greater than 200 mg daily.

Table 11: Dose Modifications for Concomitant Use With Strong CYP3A4 Inhibitors or Fluconazole

For patients coadministered strong CYP3A4 inhibitors or doses of less than or equal to 200 mg of fluconazole	Recommended JAKAFI XR Dose Modification
Starting dose for patients with MF with a platelet count:	
• Greater than or equal to 100×10^9/L	22 mg once daily
• 50×10^9/L to less than 100×10^9/L	Do not use JAKAFI XR
Starting dose for patients with PV:	11 mg once daily
If on stable dose for patients with MF or PV:	
• JAKAFI XR: Greater than or equal to 22 mg once daily	Reduce dose by 50% (round up to the closest available tablet strength)
• JAKAFI XR: 11 mg once daily	Avoid strong CYP3A4 inhibitor or fluconazole treatment or interrupt JAKAFI treatment for the duration of strong CYP3A4 inhibitor or fluconazole use
Starting dose for patients with aGVHD:	

For patients coadministered strong CYP3A4 inhibitors or doses of less than or equal to 200 mg of fluconazole	Recommended JAKAFI XR Dose Modification
Fluconazole doses of less than or equal to 200 mg	Do not use JAKAFI XR
Other CYP3A4 inhibitors	Monitor blood counts more frequently for toxicity and modify the JAKAFI XR dosage for adverse reactions if they occur *[see Dosage and Administration (2.4, 2.5)]*.
Starting dose for patients with cGVHD	
Fluconazole doses of less than or equal to 200 mg	JAKAFI XR 11 mg once daily
Other CYP3A4 inhibitors	Monitor blood counts more frequently for toxicity and modify the JAKAFI XR dosage for adverse reactions if they occur *[see Dosage and Administration (2.4, 2.5)]*.

Dose Modifications for Renal or Hepatic Impairment

Moderate to Severe Renal Impairment or End-Stage Renal Disease (ESRD) on Dialysis

Modify the JAKAFI XR dosage for patients with moderate (creatinine clearance [CLcr] 30 to 59 mL/min) to severe (CLcr 15 to 29 mL/min) renal impairment or ESRD on dialysis according to Table 12. Avoid use of JAKAFI XR in patients with ESRD (CLcr less than 15 mL/min) not requiring dialysis *[see Use in Specific Populations (8.6)]*.

Table 12: Dose Modifications for Renal Impairment

Renal Impairment Status	Platelet Count	JAKAFI XR Recommended Starting Dosage
Patients with MF		
Moderate or Severe	Greater than 150×10^9/L	No dose adjustment
	100 to 150×10^9/L	JAKAFI XR 22 mg once daily
	50 to less than 100×10^9/L	Do not use JAKAFI XR
	Less than 50×10^9/L	Avoid use *[see Use in Specific Populations (8.6)]*
ESRD on dialysis	100 to 200×10^9/L	Do not use JAKAFI XR
	Greater than 200×10^9/L	Do not use JAKAFI XR
Patients with PV		
Moderate or Severe	Any	JAKAFI XR 11 mg once daily
ESRD on dialysis	Any	Do not use JAKAFI XR
Patients with aGVHD		
Moderate or Severe	Any	Do not use JAKAFI XR
ESRD on dialysis	Any	Do not use JAKAFI XR
Patients with cGVHD		

Renal Impairment Status	Platelet Count	JAKAFI XR Recommended Starting Dosage
Moderate or Severe	Any	JAKAFI XR 11 mg once daily
ESRD on dialysis	Any	Do not use JAKAFI XR

Hepatic Impairment

Modify the JAKAFI XR dosage for patients with hepatic impairment according to Table 13.

Table 13: Dose Modifications for Hepatic Impairment

Hepatic Impairment Status	Platelet Count	JAKAFI XR Recommended Starting Dosage
Patients with MF		
Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Greater than 150×10^9/L	No dose adjustment
	100×10^9/L to 150×10^9/L	22 mg once daily
	50 to less than 100×10^9/L	Do not use JAKAFI XR
	Less than 50×10^9/L	Avoid use *[see Use in Specific Populations (8.7)]*
Patients with PV		
Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Any	11 mg once daily
Patients with aGVHD		
Mild, Moderate, or Severe based on National Cancer Institute (NCI) criteria without liver GVHD	Any	No dose adjustment
Stage 1, 2 or 3 Liver aGVHD	Any	No dose adjustment
Stage 4 Liver aGVHD	Any	Do not use JAKAFI XR
Patients with cGVHD		
Mild, Moderate, or Severe based on NCI criteria without liver GVHD	Any	No dose adjustment
Score 1 or 2 Liver cGVHD	Any	No dose adjustment
Score 3 Liver cGVHD	Any	Monitor blood counts more frequently for toxicity and modify the JAKAFI XR dosage for adverse reactions if they occur *[see Dosage and Administration (2.4, 2.5)].*

Pharmacy Communication:

Medication Order:

Medication: Ruxolitinib extended-release tablets

- 11 mg extended-release tablets - round and light pink with “I” on one side and “11” on the other
- 22 mg extended-release tablets - round and light yellow with “I” on one side and “22” on the other
- 33 mg extended-release tablets - round and pink with “I” on one side and “33” on the other
- 44 mg extended-release tablets - round and grey with “I” on one side and “44” on the other
- 55 mg extended-release tablets - round and yellow with “I” on one side and “55” on the other

Physician Communication Order:

JAKAFI XR

The recommended starting dose of JAKAFI XR is 11 mg given orally once daily. Consider increasing the dose to 22 mg once daily after at least 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with JAKAFI XR.

Treatment Completion

Consider tapering JAKAFI XR after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper JAKAFI XR by one dose level approximately every 8 weeks using the dose levels shown in Table 8. If aGVHD signs or symptoms recur during or after the taper of JAKAFI XR, consider retreatment.

Please see Important Safety Information throughout and the Full Prescribing Information for JAKAFI/JAKAFI XR.

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