

# **JAKAVI®**

## **(Ruxolitinib)**

### **Description and composition**

#### **Pharmaceutical form(s)**

5 mg tablets: round curved white to almost white tablets with 'NVR' debossed on one side and 'L5' debossed on the other side

15 mg tablets: ovaloid curved white to almost white tablets with 'NVR' debossed on one side and 'L15' debossed on the other side

20 mg tablets: elongated curved white to almost white tablets with 'NVR' debossed on one side and 'L20' debossed on the other side

#### **Active substance(s)**

Ruxolitinib phosphate

Ruxolitinib 5 mg per tablet

Ruxolitinib 15 mg per tablet

Ruxolitinib 20 mg per tablet

#### **Active moiety**

Ruxolitinib

#### **Excipients**

Cellulose, microcrystalline; Lactose monohydrate; Magnesium stearate; Silica, colloidal anhydrous; Sodium starch glycolate (Type A); Hydroxypropylcellulose; Povidone

Each 5 mg tablet contains 71.45 mg of lactose monohydrate

Each 15 mg tablet contains 214.35 mg of lactose monohydrate

Each 20 mg tablet contains 285.80 mg of lactose monohydrate

### **Indications**

#### ***Myelofibrosis (MF)***

Jakavi® is indicated for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

#### ***Polycythemia vera (PV)***

Jakavi is indicated for the treatment of patients with polycythemia who are resistant to or intolerant of hydroxyurea.

## **Graft versus host disease (GvHD)**

Jakavi is indicated for the treatment of patients aged 12 years and older with acute graft versus host disease or chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section Pharmacodynamic properties).

## **Dosage regimen and administration**

### **Monitoring instructions**

**Blood cell counts:** a blood cell count must be performed before initiating therapy with Jakavi. Complete blood counts should be monitored every 2 to 4 weeks until doses are stabilized, and then as clinically indicated (see section Warnings and precautions).

### **Starting dose**

The recommended starting dose of Jakavi in myelofibrosis (MF) is based on platelet counts (see Table 1):

**Table 1 Starting Doses in Myelofibrosis**

Platelet count	Starting dose
Greater than 200,000/mm <sup>3</sup>	20 mg orally twice daily
100,000 to 200,000/mm <sup>3</sup>	15 mg orally twice daily
75,000 to less than 100,000/mm <sup>3</sup>	10 mg orally twice daily
50,000 to less than 75,000/mm <sup>3</sup>	5 mg orally twice daily

The recommended starting dose of Jakavi in polycythemia vera (PV) and graft-versus-host disease (GvHD) is 10 mg given orally twice daily.

### **Dose modifications**

Doses may be titrated based on efficacy and safety.

### **Myelofibrosis and Polycythemia Vera**

If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-weeks intervals.

Treatment should be interrupted for platelet counts less than 50,000/mm<sup>3</sup> or absolute neutrophil counts less than 500/mm<sup>3</sup>.

In PV, treatment should also be interrupted when hemoglobin is below 8 g/dL.

After recovery of blood counts above these levels, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of blood cell counts, including a white blood cell count differential.

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

**Table 2 Dosing Recommendations for Thrombocytopenia in myelofibrosis**

	Dose at Time of Platelet Decline				
	25 mg twice daily	20 mg twice daily	15 mg twice daily	10 mg twice daily	5 mg twice daily
Platelet Count	New Dose				
100,000 to less than 125,000/mm <sup>3</sup>	20 mg twice daily	15 mg twice daily	No change	No change	No change
75,000 to less than 100,000/mm <sup>3</sup>	10 mg twice daily	10 mg twice daily	10 mg twice daily	No change	No change
50,000 to less than 75,000/mm <sup>3</sup>	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No change
Less than 50,000/mm <sup>3</sup>	Hold	Hold	Hold	Hold	Hold

In PV, dose reduction should also be considered if hemoglobin decreases below 12 g/dL and is recommended if hemoglobin decreases below 10 g/dL.

### **Graft-versus-host disease**

Dose reductions and temporary interruptions of treatment may be needed in GvHD patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth-factors, anti-infective therapies and transfusions. One dose level reduction step is recommended (10 mg twice daily to 5 mg twice daily or 5 mg twice daily to 5 mg once daily). In patients who are unable to tolerate Jakavi at a dose of 5 mg once daily, treatment should be interrupted. Detailed dosing recommendations are provided in Table 3.

**Table 3 Dosing recommendations for patients with thrombocytopenia, neutropenia, or elevated total bilirubin in patients with graft-versus-host disease**

Laboratory Parameter	Dosing Recommendation
Platelet count <20,000/mm <sup>3</sup>	Reduce Jakavi by one dose level. If platelet count $\geq 20,000/\text{mm}^3$ within seven days, dose may be increased to initial dose level, otherwise maintain reduced dose.
Platelet count <15,000/mm <sup>3</sup>	Hold Jakavi until platelet count $\geq 20,000/\text{mm}^3$ , then

<b>Laboratory Parameter</b>	<b>Dosing Recommendation</b>
	resume at one lower dose level.
Absolute neutrophil count (ANC) ≥500/mm <sup>3</sup> to <750/mm <sup>3</sup>	Reduce Jakavi by one dose level. Resume at initial dose level if ANC >1,000/mm <sup>3</sup> .
Absolute neutrophil count <500/mm <sup>3</sup>	Hold Jakavi until ANC >500/mm <sup>3</sup> , then resume at one lower dose level. If ANC >1,000/mm <sup>3</sup> , dosing may resume at initial dose level.
Total bilirubin elevation, no liver GvHD	<p>3.0 to 5.0 x ULN: Continue Jakavi at one lower dose level until ≤3.0 x ULN.</p> <p>&gt;5.0 to 10.0 x ULN: Hold Jakavi up to 14 days until total bilirubin ≤3.0 x ULN. If total bilirubin ≤3.0 x ULN dosing may resume at current dose. If not ≤3.0 x ULN after 14 days, resume at one lower dose level.</p> <p>&gt;10.0 x ULN: Hold Jakavi until total bilirubin ≤3.0 x ULN, then resume at one lower dose level.</p>
Total bilirubin elevation, liver GvHD	>3.0 x ULN: Continue Jakavi at one lower dose level until total bilirubin ≤3.0 x ULN.

#### ***Administration instruction***

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

Treatment of MF and PV may be continued as long as the benefit:risk ratio remains positive.

In GvHD, tapering of Jakavi may be considered in patients with a response and after having discontinued corticosteroids. A 50% dose reduction of Jakavi every two months is recommended. If signs or symptoms of GvHD reoccur during or after the taper of Jakavi, re-escalation of treatment should be considered.

#### ***Dose adjustment with concomitant strong CYP3A4 Inhibitors or fluconazole:***

When Jakavi is administered with strong CYP3A4 inhibitors in MF and PV patients or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) in MF, PV or GvHD patients the unit dose of Jakavi should be reduced by approximately 50%, to be

administered twice daily. The concomitant use Jakavi with fluconazole doses of greater than 200 mg daily should be avoided (see section Interactions).

More frequent monitoring (e.g. twice a week) of hematology parameters and clinical signs and symptoms of Jakavi related adverse drug reactions (ADRs) is recommended while on CYP3A4 inhibitor or dual inhibitors of CYP2C9 and CYP3A4 enzymes.

## **Special populations**

### **Renal impairment**

No specific dose adjustment is needed in patients with mild or moderate renal impairment.

In patients with severe renal impairment (creatinine clearance less than 30 mL/min) the recommended starting dose based on platelet counts for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV and GvHD patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/Pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15 – 20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup>. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for patients with platelet count >200,000/mm<sup>3</sup>. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV and GvHD patients with ESRD on hemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis and with careful monitoring of safety and efficacy (see section Clinical Pharmacology).

These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration.

### **Hepatic impairment**

In MF and PV patients with any hepatic impairment the recommended starting dose should be reduced by approximately 50% to be administered twice daily. In MF patients this reduction should be based on platelet counts. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilized. Jakavi dose can be titrated to reduce the risk of cytopenia.

In GvHD patients with any hepatic impairment including liver GvHD, no starting dose modification is recommended. See section Clinical pharmacology.

In patients with GvHD liver involvement and an increase of total bilirubin to  $>3$  x ULN, blood counts should be monitored more frequently for toxicity and a dose reduction by one dose level may be considered.

### **Treatment discontinuation**

Treatment may be continued as long as the benefit-risk remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy.

It is recommended that, for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

### **Pediatrics**

The safety and efficacy of Jakavi in pediatric patients with MF and PV have not been established.

In pediatric patients (12 years of age and older) with GvHD, the safety and efficacy of Jakavi are supported by evidence from the randomized phase 3 studies REACH2 and REACH3. The Jakavi dose in pediatric patients with GvHD aged 12 years and older is the same as in adults. The safety and efficacy of Jakavi have not been established in patients less than 12 years of age.

### **Geriatrics**

No additional dose adjustments are recommended for elderly patients.

### **Method of administration**

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

### **Contraindications**

Hypersensitivity to the active substance or any of the excipients.

### **Warnings and precautions**

#### **Decrease in blood cell count**

Treatment with Jakavi can cause hematological adverse drug reactions (ADRs), including thrombocytopenia, anemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi (for monitoring frequency see section Dosage regimen and administration). Treatment should be discontinued

in patients with platelet count less than 50,000 mm<sup>3</sup> or absolute neutrophil count less than 500/mm<sup>3</sup>.

It has been observed that MF patients with low platelet counts (<200,000/mm<sup>3</sup>) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakavi. However, platelet transfusions may be required as clinically indicated (see sections Dosage regimen and administration, and Adverse drug reactions).

Patients developing anemia may require blood transfusions. Dose modifications or interruption for patients developing anemia may also need to be considered.

Patients with haemoglobin level below 10.0 g/dl at the beginning of treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (Absolute Neutrophil Count (ANC) <500/mm<sup>3</sup>) was generally reversible and was managed by temporarily withholding Jakavi (see sections Dosage regimen and administration, and Adverse drug reactions).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections Dosage regimen and administration, and Adverse drug reactions).

## **Infections**

Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with Jakavi. Patients should be assessed for the risk of developing serious infections. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and appropriate treatment should be initiated promptly. Jakavi therapy should not be started until active serious infections have resolved.

Tuberculosis has been reported in patients receiving Jakavi. Before starting treatment, patients should be evaluated for active and inactive ('latent') tuberculosis, as per local recommendations.

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi 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.

## **Herpes zoster**

Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

## **Progressive multifocal leukencephalopathy**

Progressive multifocal leukencephalopathy (PML) has been reported with Jakavi treatment. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded.

## **Non-melanoma skin cancer**

Non-melanoma skin cancers (NMSCs) including basal cell, squamous cell, and Merkel cell carcinoma have been reported in patients treated with Jakavi. Most of the MF and PV patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to Jakavi has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

## **Lipid abnormalities/elevations**

Treatment with Jakavi has been associated with increases in lipid parameters including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Lipid monitoring and treatment of dyslipidemia according to clinical guidelines is recommended.

## **Special populations**

### **Renal impairment**

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with ESRD on dialysis the starting dose should be based on platelet counts for MF patients, while the recommended starting dose is a single dose of 10 mg for PV and GvHD patients. Subsequent doses for MF, PV and GvHD patients should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy (see section Dosage regimen and administration and section Clinical pharmacology, Special populations).

### **Hepatic impairment**

The starting dose of Jakavi should be reduced by approximately 50% in MF and PV patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the drug. In GvHD patients with hepatic impairment no modification in starting dose is needed (see section Dosage regimen and administration and Clinical pharmacology, Special populations).

### **Interactions**

If Jakavi is to be co-administered with strong CYP3A4 inhibitors in MF and PV or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole) in MF, PV, and GvHD patients, the unit dose should be reduced by approximately 50%, to be administered twice daily (for monitoring frequency see sections Dosage regimen and administration and Interactions).

## **Withdrawal effects**

After discontinuation of Jakavi treatment, MF related symptoms are expected to return. There have been cases of patients discontinuing Jakavi who experienced severe adverse events (AEs), particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of Jakavi contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered.

## **Excipients**

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicinal product.

## **Adverse drug reactions**

### **Summary of the safety profile**

#### **Myelofibrosis**

The safety of Jakavi in MF patients was evaluated using long term follow-up data from the two phase 3 studies COMFORT-I and COMFORT-II including data from patients initially randomized to Jakavi (n=301) and patients who received Jakavi after crossing over from control treatments (n=156). The median exposure upon which the ADR frequency categories for MF patients are based was 30.5 months (range 0.3 to 68.1 months).

The most frequently reported ADRs were anaemia (83.8%) and thrombocytopenia (80.5%).

Hematological ADRs (any CTCAE grade; Common Terminology Criteria for Adverse Events) included anaemia (83.8%), thrombocytopenia (80.5%) and neutropenia (20.8%). Anemia, thrombocytopenia and neutropenia are dose related effects.

The most frequent non-haematological ADRs were bruising (33.3%), dizziness (21.9%) and urinary tract infections (21.4%).

The most frequent non-haematological laboratory abnormalities identified as ADRs were increased ALT (40.7%), increased AST (31.5%) and hypertriglyceridemia (25.2%). However, no CTCAE grade 3 or 4 hypertriglyceridemia and increased AST or grade 4 increased ALT were observed.

Discontinuation due to AEs, regardless of causality, was observed in 30.0% of patients treated with Jakavi.

#### **Polycythemia vera**

The safety of Jakavi in PV patients was evaluated using long-term follow-up data from the two phase 3 studies RESPONSE and RESPONSE 2 including data from patients initially randomised to Jakavi (n=184) and patients who received Jakavi after crossing over from control treatments (n=156). The median exposure upon which the ADR frequency categories for PV patients are based was 41.7 months (range 0.03 to 59.7 months).

The most frequently reported ADRs were anaemia (61.8%) and increased ALT (45.3%).

Hematological ADRs (any CTCAE grade) included anemia (61.8%), thrombocytopenia (25.0%) and neutropenia (5.3%). Anaemia or thrombocytopenia Grade 3 and 4 were reported in respectively 2.9% or 2.6% of the patients, respectively.

The most frequent non-haematological ADRs were weight gain (20.3%), dizziness (19.4%), and headache (17.9%).

The most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as ADRs were increased ALT (45.3%), increased AST (42.6%), and hypercholesterolaemia (34.7%). The majority were Grade 1 to 2, one CTCAE Grade 4 ‘increased AST’.

Discontinuation due to AEs, regardless of causality, was observed in 19.4% of patients treated with Jakavi.

### **Acute GvHD**

The safety of Jakavi in acute GvHD patients was evaluated in the phase 3 study REACH2, including data from patients initially randomized to Jakavi (n=152) and patients who received Jakavi after crossing over from control treatment (n=49). The median exposure upon which the ADR frequency categories were based was 8.9 weeks (range 0.3 to 66.1 weeks).

The most frequently reported overall ADRs were thrombocytopenia (85.2%), anaemia (75.0%) and neutropenia (65.1%).

Hematological laboratory abnormalities identified as ADRs included thrombocytopenia (85.2%), anaemia (75.0%) and neutropenia (65.1%). Grade 3 anemia was reported in 47.7% of patients (Grade 4 not applicable per CTCAE v4.03). Grade 3 and 4 thrombocytopenia were reported in 31.3% and 47.7% of patients, respectively.

The most frequent non-hematological ADRs were cytomegalovirus (CMV) infection (32.3%), sepsis (25.4%) and UTI (17.9%).

The most frequent non-hematological laboratory abnormalities identified as ADRs were increased ALT (54.9%), increased AST (52.3%) and hypercholesterolaemia (49.2%). The majority were of grade 1 and 2.

Discontinuation due to AEs, regardless of causality, was observed in 29.4% of patients treated with Jakavi.

### **Chronic GvHD**

The safety of Jakavi in chronic GvHD patients was evaluated in the phase 3 study REACH3, including data from patients initially randomized to Jakavi (n=165) and patients who received Jakavi after crossing over from best available treatment (BAT) [n=61]. The median exposure upon which the ADR frequency categories were based was 41.4 weeks (range 0.7 to 127.3 weeks).

The most frequently reported overall ADRs were anaemia (68.6%), hypercholesterolemia (52.3%) and increased AST (52.2%).

Hematological laboratory abnormalities identified as ADRs included anemia (68.6%), thrombocytopenia (34.4%) and neutropenia (36.2%). Grade 3 anemia was reported in 14.8%

of patients (Grade 4 not applicable per CTCAE v4.03). Grade 3 and 4 neutropenia were reported in 9.5% and 6.7% of patients, respectively.

The most frequent non-hematological ADRs were hypertension (15.0%), headache (10.2%) and UTI (9.3%).

The most frequent non-hematological laboratory abnormalities identified as ADRs were hypercholesterolemia (52.3%), increased AST (52.2%) and increased ALT (43.1%). The majority were Grade 1 and 2. Discontinuation due to AEs, regardless of causality, was observed in 18.1% of patients treated with Jakavi.

### Tabulated summary of adverse drug reactions from clinical trials

ADRs from clinical trials in MF and PV are listed in Table 4. ADRs from clinical trials in acute and chronic GvHD are listed in Table 5. All ADRs are listed by MedDRA system organ class (SOC). Within each SOC, the ADRs are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each ADR is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

In the clinical studies program the severity of ADRs was assessed based on the CTCAE defining Grade 1=mild, Grade 2= moderate, Grade 3=severe and Grade 4=life-threatening or disabling, Grade 5=death.

**Table 4 ADRs reported in the phase 3 studies in MF and PV**

Adverse drug reactions and CTCAE Grade <sup>3</sup>	Frequency category for MF patients	Frequency category for PV patients
	Long-term follow-up data Week 256: COMFORT-I Week 256: COMFORT-II	Long-term follow-up data Week 256: RESPONSE Week 156: RESPONSE-2
<b>Infections and infestations</b>		
Urinary Tract infections	Very common	Very common
Herpes zoster	Very common	Very common
Pneumonia	Very common	Common
Tuberculosis	Uncommon	-
<b>Blood and lymphatic system disorders</b>		
Anemia <sup>1</sup>		
CTCAE <sup>1</sup> Grade 4 ( $<6.5\text{g/dL}$ )	Very common	Uncommon
CTCAE Grade 3 ( $<8.0$ to $6.5\text{g/dL}$ )	Very common	Common
Any CTCAE Grade	Very common	Very common
Thrombocytopenia <sup>1</sup>		
CTCAE Grade 4 ( $<25,000/\text{mm}^3$ )	Common	Uncommon
CTCAE Grade 3	Very common	Common

Adverse drug reactions and CTCAE Grade <sup>3</sup>	Frequency category for MF patients	Frequency category for PV patients
	Long-term follow-up data Week 256: COMFORT-I Week 256: COMFORT-II	Long-term follow-up data Week 256: RESPONSE Week 156: RESPONSE-2
(50,000 to 25,000/mm <sup>3</sup> ) Any CTCAE Grade	Very common	Very common
Neutropenia <sup>1</sup>		
CTCAE Grade 4 (<500/mm <sup>3</sup> )	Common	Uncommon
CTCAE Grade 3 (<1000 to 500/mm <sup>3</sup> )	Common	Uncommon
Any CTCAE Grade	Very common	Common
Pancytopenia <sup>2</sup>	Common	Common
<b>Metabolism and nutrition disorders</b>		
Hypercholesterolaemia <sup>1</sup>		
Any CTCAE Grade	Very common	Very common
Hypertriglyceridaemia <sup>1</sup>		
CTCAE Grade 1	Very common	Very common
Weight gain	Very common	Very common
<b>Nervous system disorders</b>		
Dizziness	Very common	Very common
Headache	Very common	Very common
<b>Gastrointestinal disorders</b>		
Constipation	Very common	Very Common
Flatulence	Common	Common
<b>Skin and subcutaneous tissue disorders</b>		
Bruising	Very common	Very common
<b>Hepatobiliary disorders</b>		
Increased ALT <sup>1</sup>		
CTCAE Grade 3 (> 5x to 20 x ULN)	Common	Common
Any CTCAE Grade	Very common	Very common
Increased AST <sup>1</sup>		
Any CTCAE Grade	Very common	Very common
<b>Vascular disorders</b>		
Hypertension	Very common	Very common

<sup>1</sup> Frequency is based on new or worsened laboratory abnormalities compared to baseline.

<sup>2</sup> Pancytopenia is defined as hemoglobin level <100 g/L, platelet count <100 x 10<sup>9</sup>/L, and neutrophils count <1.5 x 10<sup>9</sup>/L (or low WBC count of Grade 2 if neutrophils count is missing), simultaneously in the same laboratory assessment.

<sup>3</sup> CTCAE Version 3.0;

Upon discontinuation MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In MF

clinical studies the total symptom score for MF symptoms gradually returned to baseline values within 7 days after dose discontinuation.

**Table 5 ADRs reported in the phase 3 studies in GvHD**

ADR	Acute GvHD (REACH2) (N=201)			Chronic GvHD (REACH3) (N=226)		
	Frequency category	All grades (%)	CTCAE <sup>3</sup> Grade 3 / 4 (%)	Frequency category	All grades (%)	CTCAE <sup>3</sup> Grade 3 / 4 (%)
<b>Infections and infestations</b>						
CMV infections	Very common	32.3	10.9 / 0.5	-	-	- / -
Sepsis	Very common	25.4	4.0 / 17.9 <sup>4</sup>	-	-	- / -
Urinary tract infections	Very common	17.9	6.0 / 0.5	Common	9.3	1.3 / 0
BK virus infections	-	-	- / -	Common	4.9	0.4 / 0
<b>Blood and lymphatic system disorders</b>						
Thrombocytopenia <sup>1</sup>	Very common	85.2	31.3 / 47.7	Very common	34.4	5.9 / 10.7
Anaemia <sup>1</sup>	Very common	75.0	47.7 / NA	Very common	68.6	14.8 / NA
Neutropenia <sup>1</sup>	Very common	65.1	17.9 / 20.6	Very common	36.2	9.5 / 6.7
Pancytopenia <sup>1,2</sup>	Very common	32.8	NA	-	-	- / -
<b>Metabolism and nutrition disorders</b>						
Hypercholesterolaemia <sup>1</sup>	Very common	49.2	3.3 / 5.9	Very common	52.3	5.5 / 0.5
Weight gain	-	-	-	Common	3.5	0 / 0
<b>Nervous system disorders</b>						
Headache	Common	8.5	0.5 / 0	Very common	10.2	1.3 / 0
<b>Vascular disorders</b>						
Hypertension	Very common	13.4	5.5 / 0	Very common	15.0	5.3 / 0
<b>Gastrointestinal disorders</b>						
Increased lipase <sup>1</sup>	-	-	-	Very common	35.9	9.5 / 0.4
Increased amylase <sup>1</sup>	-	-	-	Very common	32.4	4.2 / 2.7
Nausea	Very common	16.4	0.5 / 0	-	-	- / -
Constipation	-	-	-	Common	6.6	0 / 0
<b>Hepatobiliary disorders</b>						
Increased ALT <sup>1</sup>	Very common	54.9	17.6 / 1.5	Very common	43.1	4.7 / 0.9
Increased AST <sup>1</sup>	Very common	52.3	7.8 / 0	Very common	52.2	3.1 / 0.9

	Acute GvHD (REACH2) (N=201)			Chronic GvHD (REACH3) (N=226)		
ADR	Frequency category	All grades (%)	CTCAE <sup>3</sup> Grade 3 / 4 (%)	Frequency category	All grades (%)	CTCAE <sup>3</sup> Grade 3 / 4 (%)
<b>Musculoskeletal and connective tissue disorders</b>						
Increased blood CPK <sup>1</sup>	-	-	-	Very common	31.1	1.0 / 1.4
<b>Renal and urinary disorders</b>						
Increased blood creatinine <sup>1</sup>	-	-	-	Very common	38.4	1.3 / 0

<sup>1</sup> Frequency is based on new or worsened laboratory abnormalities compared to baseline.  
<sup>2</sup> Pancytopenia is defined as hemoglobin level <100 g/L, platelet count <100 x 10<sup>9</sup>/L, and neutrophils count <1.5 x 10<sup>9</sup>/L (or low WBC of grade 2 if neutrophil count is missing), simultaneously in the same laboratory assessment. No CTCAE grades defined.  
<sup>3</sup> CTCAE Version 4.03.  
<sup>4</sup> Grade 4 sepsis includes 16 (8%) Grade 4 events and 20 (10%) Grade 5 events.

### ADRs from spontaneous reports and literature cases (frequency not known)

Tuberculosis as an ADR has been observed post-marketing with Jakavi in PV patients via spontaneous case reports and in the literature. Because cases were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency, which is therefore characterized as 'not known'.

### Description of selected adverse drug reactions

#### Anemia

In phase 3 MF clinical studies, median time to onset of first CTCAE grade 2 or higher anemia was 1.5 months. One patient (0.3%) discontinued treatment because of anemia.

In patients receiving Jakavi mean decreases in hemoglobin reached a nadir of approximately 15 to 20 g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 10 g/L below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomized, placebo controlled study COMFORT-I, 59.4% of Jakavi treated patients and 37.1% of patients receiving placebo received red blood cell transfusions during randomized treatment. In the COMFORT-II study, the rate of packed red blood cell transfusions was 51.4% in the Jakavi arm and 38.4% in the best available therapy arm (BAT).

Over the randomized period in the RESPONSE and RESPONSE-2 studies, anaemia was less frequent in PV patients (40.8%) versus 82.4% in MF patients. The frequency of CTCAE Grade 3 and 4 events was 1.1% in PV patients, while in the MF patients, the frequency was 42.5%.

In the phase 3 acute and chronic GvHD studies, anemia CTCAE Grade 3 was reported in 47.7% and 14.8% of patients, respectively.

## **Thrombocytopenia**

In the phase 3 MF-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 50,000/mm<sup>3</sup> was 14 days. During the randomized period, platelet transfusions were administered to 4.5% of patients receiving Jakavi and to 5.8% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm<sup>3</sup> to 200,000/mm<sup>3</sup> before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm<sup>3</sup> (64.2% versus 35.4%).

Over the randomized period in the RESPONSE and RESPONSE-2 studies, the rate of patients experiencing thrombocytopenia was lower in PV (16.8%) compared to MF (69.8%) patients. The frequency of severe (i.e. of CTCAE Grade 3 and 4) thrombocytopenia was lower in PV (3.3%) than in MF (11.6%) patients.

In the phase 3 acute GvHD study, Grade 3 and 4 thrombocytopenia was observed in 31.3% and 47.7% of patients, respectively. In the phase 3 chronic GvHD study Grade 3 and 4 thrombocytopenia was lower (5.9% and 10.7%) than in acute GvHD.

## **Neutropenia**

In the phase 3 MF clinical studies, in patients who developed grade 3 or 4 neutropenia, the median time of onset was 12 weeks. During the randomized period of the studies, dose holding or reductions due to neutropenia were reported in 1.3% of patients and 0.3% of patients discontinued treatment because of neutropenia.

Over the randomized period in the RESPONSE and RESPONSE-2 studies in PV, neutropenia was observed in 3 patients (1.6%) of which one patient developed CTCAE Grade 4 neutropenia.

During the long-term follow-up, 2 patients reported CTCAE grade 4 neutropenia.

In the phase 3 acute GvHD study, Grade 3 and 4 neutropenia was observed in 17.9% and 20.6% of patients, respectively. In the phase 3 chronic GvHD study, Grade 3 and 4 neutropenia was lower (9.5% and 6.7%) than in acute GvHD.

## **Infections**

In the randomized period of the Phase 3 MF clinical studies grade 3 or 4 urinary tract infection was reported for 1.0% of patients. Urosepsis was reported in 1.0% of patients and kidney infection 1 patient. The rate of herpes zoster was 4.0%. During the long-term follow-up, herpes zoster of any grade was observed in 19.7% and 14.7% of MF and PV patients, respectively.

In the randomized period of two phase 3 PV clinical studies, one (0.5%) Grade 3/4 urinary tract infection was observed. The rate of herpes zoster was 4.3% including one report of Grade 3 and 4 post herpetic neuralgia. During the long-term follow-up, urinary tract infection of any grade were observed in 11.8% and 14.7% of patients, respectively.

In the phase 3 acute GvHD study, Grade 3 and 4 CMV infections were reported in 10.9% and 0.5% of patients, respectively. CMV infection with organ involvement was seen in very few patients; CMV colitis, CMV enteritis and CMV gastrointestinal infection of any Grade were reported in four, two and one patients, respectively.

Sepsis events including septic shock of any Grade were reported in 25.4% of patients.

In the phase 3 chronic GvHD study, Grade 3 urinary tract infections and BK virus infections were reported in 1.3% and 0.4% of patients, respectively.

### ***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: [pv-center@pom.go.id](mailto:pv-center@pom.go.id)

Phone: +62-21-4244691 Ext.1079

Website: <https://e-meso.pom.go.id/ADR>

or

Novartis Indonesia

Website: [www.novartis.com/report](http://www.novartis.com/report)

## **Interactions**

### **Agents that may alter plasma concentration of ruxolitinib**

**Strong CYP3A4 inhibitors:** in healthy subjects receiving ketoconazole, a strong CYP3A4 inhibitor, at 200 mg twice daily for four days, the AUC of ruxolitinib increased by 91% and the half-life was prolonged from 3.7 to 6.0 hours.

When administering Jakavi with strong CYP3A4 inhibitors the total daily dose of Jakavi should be reduced by approximately 50%, except in GvHD patients. The effect of strong CYP3A4 inhibitors in patients with GvHD was not found to have a significant impact on any parameter in the Population PK model.

Patients should be closely monitored for cytopenias and dose titrated based on safety and efficacy (see section Dosage regimen and administration).

**Mild or moderate CYP3A4 inhibitors:** In healthy subjects receiving erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for four days, there was a 27% increase in the AUC of ruxolitinib.

No dose adjustment is recommended when Jakavi is co administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). Patients should be closely monitored for cytopenias when initiating therapy with a moderate CYP3A4 inhibitor.

***Dual moderate CYP2C9 and CYP3A4 inhibitors (e.g. Fluconazole):*** in healthy subjects receiving fluconazole, a dual CYP2C9 and CYP3A4 inhibitor, as a single 400 mg dose followed by 200 mg once daily for seven days, there was a 232% increase in the AUC of ruxolitinib. A 50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes. The concomitant use of Jakavi with fluconazole doses of greater than 200 mg daily should be avoided.

***CYP3A4 inducers:*** Patients should be closely monitored and the dose titrated based on safety and efficacy. Upon initiation of a CYP3A4 inducer, no dose adjustment is recommended. Gradual dose increases of Jakavi may be considered if the effectiveness of therapy is diminished during treatment with a CYP3A4 inducer.

In healthy subjects receiving rifampin, a potent CYP3A4 inducer, at 600 mg once daily for ten days, the AUC of ruxolitinib following a single dose decreased by 71% and the half-life decreased from 3.3 to 1.7 hours. The relative amount of active metabolites increased in relation to parent compound.

### **Effects of ruxolitinib on other medicinal products**

#### **Substances transported by P-glycoprotein or other transporters**

Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased systemic exposure of substrates of these transporters such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic Drug Monitoring (TDM) or clinical monitoring of the affected substance is advised.

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimized if the time between administrations is kept apart as long as possible.

#### **Haematopoietic growth factors**

The concurrent use of haematopoietic growth factors and Jakavi has not been studied. It is not known whether the Janus Associated Kinase (JAK) inhibition by Jakavi reduces the efficacy of the haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of Jakavi.

#### **Cytoreductive therapies**

The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co administration is unknown.

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing

ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

## **Pregnancy, lactation, females and males of reproductive potential**

### **Pregnancy**

#### **Risk summary**

There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits have demonstrated ruxolitinib-induced embryotoxicity and fetotoxicity. Following prenatal exposure, increases in post-implantation loss in rabbits and reduced fetal weights in rats and rabbits were observed. In rats and rabbits these effects occurred at exposures approximately 2-fold and 0.07-fold, respectively, relative to clinical exposure at the maximum human recommended dose of 25 mg b.i.d based on AUC.

The use of Jakavi during pregnancy is not recommended. The patient should be advised of the risk to fetus if Jakavi is used during pregnancy or if the patient becomes pregnant while taking this medicinal product.

### **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 was no evidence of teratogenicity. However, 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 9% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 0.07 times 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 embryo-fetal survival, growth and development parameters at the highest dose evaluated (0.3 times the clinical exposure at the maximum recommended dose of 25 mg twice daily).

### **Lactation**

#### **Risk Summary**

It is not known if ruxolitinib is transferred to human milk. There are no data on the effects of ruxolitinib on the breast-fed child or the effects of ruxolitinib on milk production. Ruxolitinib and/or its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse drug reactions in nursing infants from Jakavi, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance

of the drug to the mother. It is recommended that women should not breast-feed during treatment with Jakavi.

## **Data**

### **Animal data**

In lactating rats administered a single dose of 30 mg/kg, exposure to ruxolitinib was 13-fold higher in milk than the maternal plasma.

### **Females and males of reproductive potential**

#### **Contraception**

Females of reproductive potential should be advised that animal studies have been performed showing ruxolitinib to be harmful to the developing fetus. Sexually active females of reproductive potential should use effective contraception (methods that result in <1% pregnancy rates) during treatment with Jakavi.

#### **Infertility**

In animal studies, no effects were observed on fertility or reproductive performance of male or female rats. In a pre- and postnatal study in rats, fertility in the first generation offspring was also not affected.

## **Overdosage**

There is no known antidote for overdoses with Jakavi. 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 ruxolitinib.

## **Clinical pharmacology**

### **Pharmacotherapeutic group, ATC**

ATC code L01XE-18 (protein kinase inhibitors)

### **Mechanism of action (MOA)**

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC<sub>50</sub> values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells.

MF and PV are a myeloproliferative neoplasm (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signaling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signaling and cell proliferation of cytokine-dependent cellular models of hematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC<sub>50</sub>'s ranging from 80-320 nM. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen, decreased circulating inflammatory cytokines (eg, TNF-alpha, IL-6) and resulted in significantly prolonged survival in the mice at doses that did not cause myelosuppressive effects.

JAK-STAT signaling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GvHD pathogenesis. In a mouse model of acute GvHD, oral administration of ruxolitinib was associated with decreased expression of inflammatory cytokines in colon homogenates and reduced immune-cell infiltration in the colon.

## **Pharmacodynamics (PD)**

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects and MF and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and MF patients, indicating no accumulation of either parent or active metabolites.

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF-alpha, IL-6, and CRP in patients with MF were decreased following treatment with Jakavi. Patients with MF did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with Jakavi.

In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

## **Pharmacokinetics (PK)**

### **Absorption**

Ruxolitinib is a Class 1 molecule under the Biopharmaceutical Classification System, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (C<sub>max</sub>) achieved approximately 1 hour post-dose. Based on a mass balance study in humans,

oral absorption of ruxolitinib was 95% or greater. Mean ruxolitinib  $C_{max}$  and total exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. There was no clinically relevant change in the PK of ruxolitinib upon administration with a high-fat meal. The mean  $C_{max}$  was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) upon dosing with a high-fat meal.

## **Distribution**

The mean volume of distribution at steady state is approximately 72 L in MF patients with an inter-subject variability of 29.4% and 75 L in PV patients with an associated inter-subject variability of 22.6%. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins in vitro is approximately 97%, mostly to albumin. A whole body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

## **Biotransformation/metabolism**

In vitro studies indicate that CYP3A4 and CYP2C9 are the major enzymes responsible for metabolism of ruxolitinib. Parent compound is the predominant entity in humans representing approximately 60% of the drug-related material in circulation. Two major and active metabolites were identified in plasma of healthy subjects representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum of all active metabolites contribute to 18% of the overall pharmacodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on in vitro studies.

## **Elimination**

Following a single oral dose of [ $^{14}C$ ] ruxolitinib in healthy adult subjects, 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. The mean elimination half-life of ruxolitinib is approximately 3 hours.

## **Linearity/non-linearity**

Dose proportionality was demonstrated in the single and multiple dose studies.

## **Special populations**

### **Effects of age, gender, or race**

Based on studies in healthy subjects, no relevant differences in ruxolitinib PK were observed with regard to gender and race. In a population PK evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. Clearance was 17.7 L/h in women and 22.1 L/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 L/h in PV patients, with a 42% inter-subject variability, and no relationship was apparent between oral clearance and gender, patient age or race in this patient population.

## Pediatric

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

### Renal impairment

Following a single Jakavi dose of 25 mg, the pharmacokinetics were similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and most markedly in the subjects with ESRD requiring hemodialysis. Ruxolitinib is not removed by dialysis. A dose modification is recommended for patients with severe renal impairment (Clcr less than 30 mL/min). For patients with ESRD a modification of the dosing schedule is recommended (see section Dosage regimen and administration).

### Hepatic impairment

Following a single Jakavi dose of 25 mg in patients with varying degrees of hepatic impairment, the pharmacokinetics and pharmacodynamics of ruxolitinib were assessed. The mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal hepatic function and indicating no clear relationship to the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). A dose reduction is recommended for MF and PV patients with hepatic impairment (see section Dosage regimen and administration).

Mild, moderate or severe hepatic impairment in patients with GvHD was not found to have a significant impact on any parameter in the Population PK model.

## Clinical studies

### Myelofibrosis

Two randomized Phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (Primary Myelofibrosis (PMF), Post-Polycythemia Vera Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-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 prognostic factors that comprise the IWG criteria consist of age  $>65$  years, presence of constitutional symptoms (weight loss, fever, night sweats) anemia (hemoglobin  $<10$  g/dL), leukocytosis (history of WBC  $>25 \times 10^9/L$ ) and circulating blasts  $\geq 1\%$ . The starting dose of Jakavi was based on platelet count. Patients with a platelet count between 100,000 and 200,000/mm<sup>3</sup> were started on Jakavi 15 mg twice daily and patients with a platelet count  $>200,000/\text{mm}^3$  were started on Jakavi 20 mg twice daily. Of the 301 patients, 111 (36.9%) had a baseline platelet count between 100,000 and 200,000/mm<sup>3</sup>, and 190 (63.1%) had a baseline platelet count  $>200,000/\text{mm}^3$ . Patients with platelet counts  $\leq 100,000/\text{mm}^3$  were not eligible in COMFORT studies. 69 patients were enrolled in the EXPAND study, a Phase Ib, open label, dose-finding study in patients with MF (PMF, PPV-MF or PET-MF) and baseline platelet counts  $\geq 50,000$  and  $<100,000/\text{mm}^3$ . In COMFORT studies, doses were individualized based upon tolerability and efficacy with

maximum doses of 20 mg twice daily for patients with platelet counts between 100,000 to  $\leq$ 125,000/mm<sup>3</sup>, of 10 mg twice daily for patients with platelet counts between 75,000 to  $\leq$ 100,000/mm<sup>3</sup>, and of 5 mg twice daily for patients with platelet counts between 50,000 to  $\leq$ 75,000/mm<sup>3</sup>.

COMFORT-I was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. Patients were dosed with Jakavi or matching placebo. The primary efficacy endpoint was proportion of subjects achieving  $\geq$ 35% reduction from baseline in spleen volume at Week 24 as measured by MRI or CT.

Secondary endpoints included duration of maintenance of a  $\geq$ 35% reduction from baseline in spleen volume, proportion of patients who had a  $\geq$ 50% reduction in total symptom score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, change in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary and overall survival.

COMFORT-II was an open-label, randomized study in 219 patients. Patients were randomized 2:1 to Jakavi versus BAT. BAT was selected by the investigator on a patient-by-patient basis. In the BAT arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving  $\geq$ 35% reduction from baseline in spleen volume at Week 48 as measured by MRI or CT.

A secondary endpoint in COMFORT-II was the proportion of patients achieving a  $\geq$ 35% reduction of spleen volume measured by MRI or CT from baseline to Week 24. Duration of maintenance of a  $\geq$ 35% reduction from baseline in responding patients was also a secondary endpoint.

In COMFORT-I, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 68 years with 61% of patients older than 65 years and 54% male. Fifty percent (50%) of patients had PMF, 31% had PPV-MF and 18% had PET-MF. Twenty-one percent (21%) of patients had red blood transfusions within 8 weeks of enrollment in the study. The median platelet count was 251,000/mm<sup>3</sup>. Seventy-six percent (76%) of patients had the mutation encoding the V617F substitution present in the JAK protein. Patients had a median palpable spleen length of 16 cm. At baseline 37.4% of the patients in the Jakavi arm had grade 1 anemia, 31.6% grade 2 and 4.5% grade 3, while in the placebo arm 35.8% had grade 1, 35.1% grade 2, 4.6% grade 3, and 0.7% grade 4. Grade 1 thrombocytopenia was found in 12.9 % of patients in the Jakavi arm and 13.2% in the placebo arm.

In COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 66 years with 52% of patients older than 65 years and 57% male. Fifty-three percent (53%) of the patients had PMF, 31% had PPV-MF, and 16% had PET-MF. Nineteen percent (19%) of the patients were considered transfusion dependent at baseline. Patients had a median palpable spleen length of 15 cm.

At baseline 34.2% of the patients in the Jakavi arm had grade 1 anemia, 28.8% grade 2, and 7.5% grade 3, while in the BAT arm 37% had grade 1, 27.4% grade 2, 13.7% grade 3, and 1.4% grade 4. Thrombocytopenia of grade 1 was found in 8.2% of the patients in the Jakavi arm, and 9.6% in the BAT arm. Efficacy analyses of the primary endpoint in COMFORT-I

and COMFORT-II are presented in Table 6. A significantly larger proportion of patients in the Jakavi arm achieved a  $\geq 35\%$  reduction in spleen volume from baseline in both studies compared to placebo in COMFORT-I and BAT in COMFORT-II.

**Table 6 Percent of Patients with  $\geq 35\%$  Reduction from Baseline in Spleen Volume at Week 24 in COMFORT-I and at Week 48 in COMFORT-II (ITT)**

	COMFORT-I		COMFORT-II	
	Jakavi (N=155)	Placebo (N=153)	Jakavi (N=144)	BAT (N=72)
Time Points	Week 24		Week 48	
Number (%) of Subjects with Spleen Volume Reduced by $\geq 35\%$	65 (41.9)	1 (0.7)	41 (28.5)	0
95% Confidence Intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
P-value	< 0.0001		< 0.0001	

In COMFORT-I, 41.9% of patients in the Jakavi arm achieved a  $\geq 35\%$  reduction in spleen volume from baseline compared with 0.7% in the placebo arm at Week 24. A similar proportion of patients in the Jakavi arm achieved a  $\geq 50\%$  reduction in palpable spleen length.

In COMFORT-II, 28.5% of patients in the Jakavi arm achieved a  $\geq 35\%$  reduction in spleen volume from baseline compared with none (0%) in the BAT arm at Week 48. A secondary endpoint was the proportion of patients achieving a  $\geq 35\%$  reduction of spleen volume at Week 24. A significantly larger proportion of patients in the Jakavi arm 46 patients (31.9%) achieved a  $\geq 35\%$  reduction in spleen volume from baseline compared to no (0%) patients in the BAT arm (p-value <0.0001).

A significantly higher proportion of patients in the Jakavi arm achieved a  $\geq 35\%$  reduction from baseline in spleen volume regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (PMF, PPV-MF, PET-MF).

Figure 1 shows a waterfall plot of the percent change from baseline in spleen volume at Week 24 in COMFORT-I. Among the 139 patients in the Jakavi arm who had both baseline and Week 24 spleen volume evaluations, all but two patients had some level of reduction in spleen volume at Week 24, with a median reduction of 33%. Among the 106 patients in the placebo arm who had both baseline and Week 24 spleen volume evaluations, there was a median increase of 8.5%.

**Figure 1**

**Waterfall Plot of Percent Change from Baseline in Spleen Volume at Week 24 (Observed Cases) COMFORT-I**

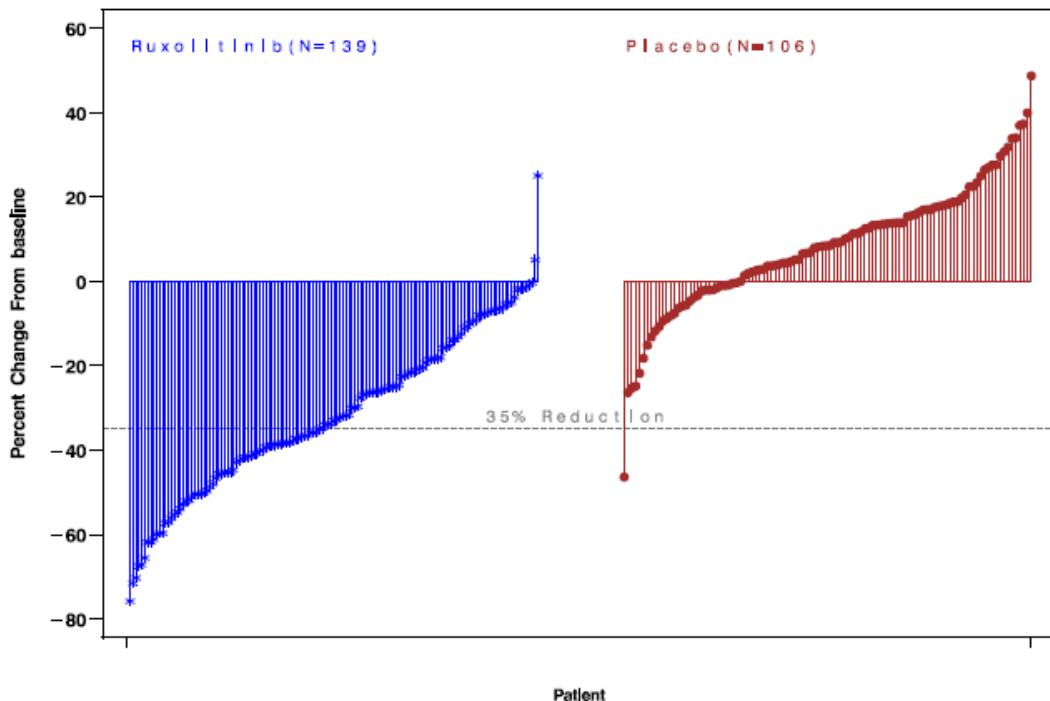
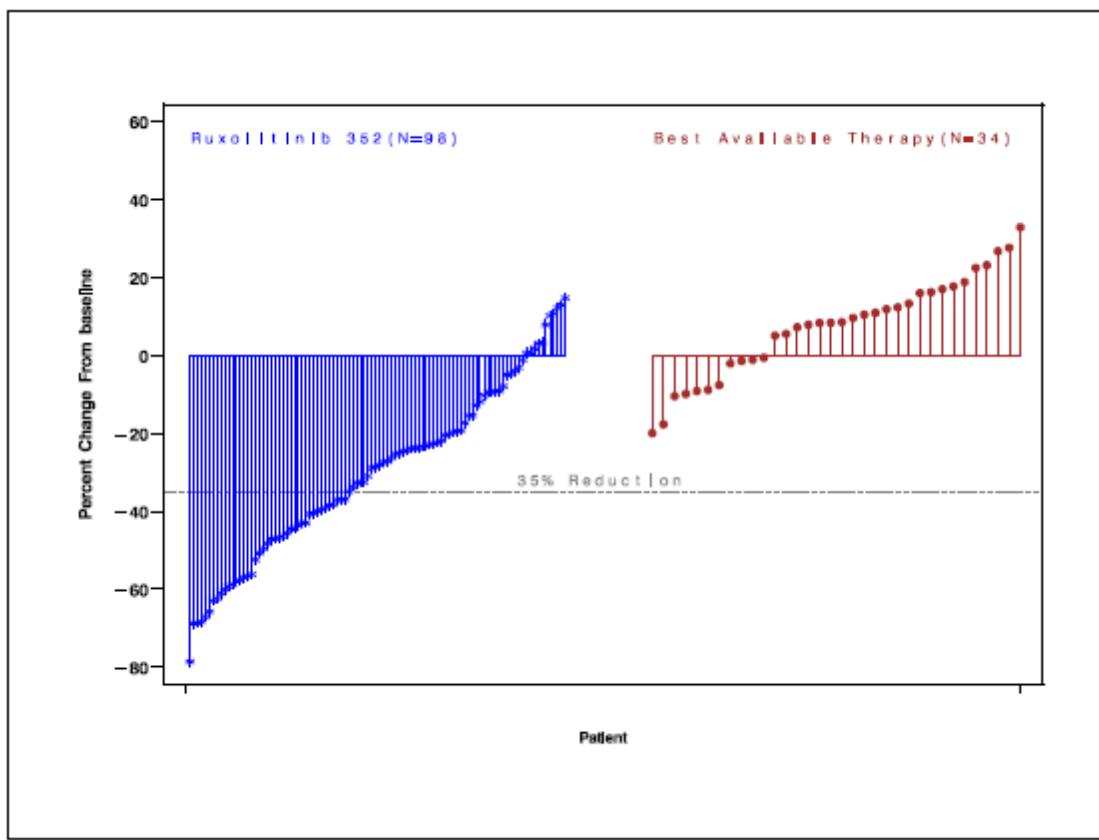


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the Jakavi arm who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was 28%. Among the 34 patients in the BAT arm who had both baseline and Week 48 spleen volume evaluations, there was a median increase of 8.5%.

**Figure 2**

**Waterfall Plot of Percent Change from Baseline in Spleen Volume at Week 48 in COMFORT-II**



The probability of duration from 1st  $\geq 35\%$  reduction of spleen volume to 25% increase from nadir and loss of response in COMFORT-I and COMFORT-II is shown in Table 7.

**Table 7 Kaplan-Meier Analysis of Duration from 1st  $\geq 35\%$  Reduction of Spleen Volume to 25% Increase from Nadir and Loss of Response in Jakavi Patients (COMFORT- I and - II)**

Statistics	Jakavi (COMFORT-I)	Jakavi (COMFORT-II)
Probability of >12 weeks of duration (95% CI)	0.98 (0.89, 1.00)	0.92 (0.82, 0.97)
Probability of >24 weeks of duration (95% CI)	0.89 (0.75, 0.95)	0.87 (0.76, 0.93)
Probability of >36 weeks of duration (95% CI)	0.71 (0.41, 0.88)	0.77 (0.63, 0.87)
Probability of >48 weeks of duration (95% CI)	not applicable	0.52 (0.18, 0.78)

Among the 80 patients that showed a  $\geq 35\%$  reduction at any time point in COMFORT-I and of the 69 patients in COMFORT-II, the probability that a patient would maintain a response on Jakavi for at least 24 weeks was 89% and 87% in COMFORT-I and COMFORT-II respectively and the probability of maintaining a response for at least 48 weeks was 52% in COMFORT-II.

Jakavi improved MF-related symptoms and quality of life (QOL) in patients with PMF, PPV-MF and PET-MF. In COMFORT-I symptoms of MF were captured using the modified MFSAF diary v2.0 as an electronic diary, which patients completed daily. The change from baseline in the Week 24 total score was a secondary endpoint in this study. Significantly larger proportion of patients in the Jakavi arm achieved a  $\geq 50\%$  improvement from baseline in the Week 24 total symptom score compared with the placebo group (45.9% and 5.3%, respectively,  $p < 0.0001$  using the Chi-Squared test).

An improvement in overall quality of life was measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 in COMFORT-I and COMFORT-II. COMFORT-I compared Jakavi to placebo at 24 weeks and COMFORT-II compared Jakavi to BAT at 48 weeks. At baseline for both studies, EORTC QLQ-C30 individual subscale scores for the Jakavi and comparator arms were similar. At Week 24 in COMFORT-I, the Jakavi arm showed significant improvement in the global health status/QOL of the EORTC QLQ-C30 compared with the placebo arm (mean change of +12.3 and -3.4 for Jakavi and placebo, respectively,  $p < 0.0001$ ). At week 24 and week 48, the Jakavi arm in COMFORT-II showed a trend towards greater improvement of global health status/QOL compared to BAT, an exploratory endpoint, consistent with the COMFORT-I findings.

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomized to the Jakavi arm was 27.1% (42 of 155 patients) versus 35.1% (54 of 154) in patients randomized to placebo. There was a 31.3% reduction in the risk of death in the Jakavi arm as compared to placebo (HR: 0.687; 95% CI: 0.459-1.029; p= 0.0668). At final analysis, after a median follow up of 61.7 months, the reduction in risk of death was maintained at 30.7% (HR: 0.693; 95% CI: 0.503, 0.956, p=0.025).

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomized to Jakavi was 19.9% (29 of 146 patients) versus 30.1% (22 of 73 patients) in patients randomized to BAT. There was a 52% reduction in risk of death in the Jakavi arm compared to the BAT arm (HR: 0.48; 95% CI: 0.28-0.85; p= 0.009). At final analysis, after a median follow up 55.9 months, the reduction in risk of death was consistent with COMFORT-I (HR: 0.67, 95% CI: 0.44-1.02, p=0.062).

### **Polycythemia vera**

A randomized, open-label, active-controlled Phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea. A total of 110 patients were randomized to the Jakavi arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the Jakavi arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening.

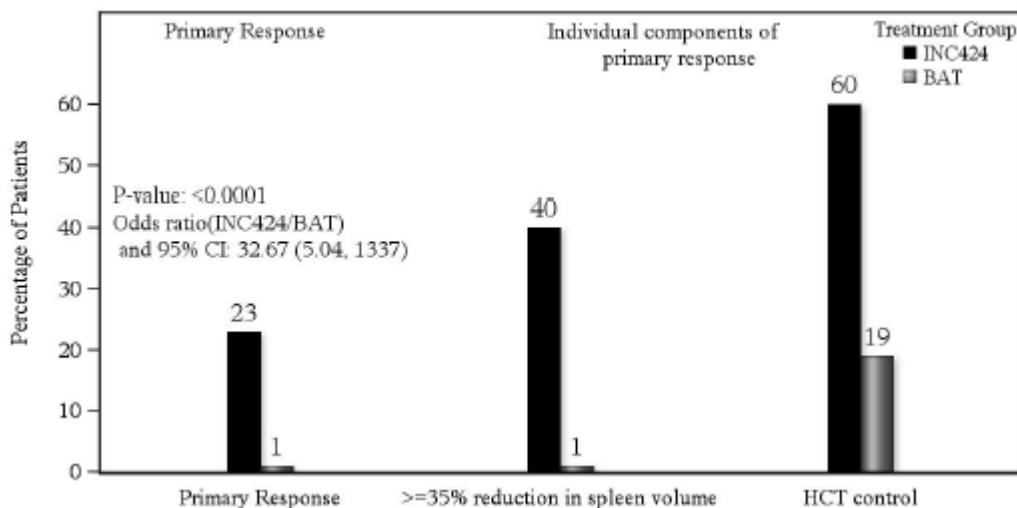
The primary composite endpoint was the proportion of patients achieving both the absence of phlebotomy eligibility (HCT control) and  $\geq 35\%$  reduction in spleen volume from baseline at Week 32. Phlebotomy eligibility was defined as a confirmed HCT  $>45\%$  that is at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT  $>48\%$ , whichever is lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and who remained free from progression at Week 48, and the proportion of patients achieving complete hematological remission at Week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi arm achieved the primary composite endpoint and each of its individual components. Significantly more patients on Jakavi (23%) compared to BAT (0.9%) achieved a primary response (p<0.0001). HCT control was achieved in 60% of patients in the Jakavi arm compared to 18.75% in the BAT arm and  $\geq 35\%$  reduction in spleen volume was achieved in 40% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 3).

Both key secondary endpoints were also met: The proportion of patients achieving a complete hematologic remission was 23.6% on Jakavi compared to 8.0% on BAT (p=0.0013), and the

proportion of patients achieving a durable primary response at week 48 was 20% on Jakavi and 0.9% on BAT ( $p<0.0001$ ).

**Figure 3 Patients achieving the Primary Endpoint and Components of the Primary Endpoint at Week 32**



Symptom burden was assessed using the MPN-Symptoms Assessment Form (SAF) total symptom score (TSS) electronic patient diary consisting of 14 questions. At Week 32, 49% and 64% of patients treated with Jakavi achieved a  $\geq 50\%$  reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. A total of 66% of Jakavi-treated patients compared to 19% in BAT reported an improvement as early as 4 weeks after the start of treatment. Improvement in perception of treatment benefit was also higher in Jakavi-treated patients at Week 32 (78% versus 33%).

Additional analyses from the RESPONSE study to assess durability of response were conducted at Week 80 and week 256 following randomization. Out of 25 patients who had achieved primary response at week 32, 3 patients had progressed by week 80 and 6 patients by week 256. The probability to have maintained a response from week 32 up to week 80 and week 256 was 92% and 74%, respectively (see Table 8)

**Table 8 Durability of Primary Response in the RESPONSE Study up to Week 256**

	Week 32	Week 80	Week 256
Primary response achieved at week 32*, n/N (%)	25/110 (23%)	n/a	n/a
Patients maintaining primary response	n/a	22/25	19/25
Probability of maintaining primary response	n/a	92%	74%

\* According to the primary response composite endpoint criteria: absence of phlebotomy eligibility (HCT control) and a  $\geq 35\%$  reduction in spleen volume from baseline.

n/a: not applicable

A second randomized, open label, active-controlled phase IIIb study (RESPONSE-2) was conducted in 149 PV patients who were resistant to or intolerant of hydroxyurea but without palpable splenomegaly. Seventy-four patients were randomized to the Jakavi arm and 75 patients to the BAT arm. The starting dose and dose adjustments of Jakavi and investigator-selected BAT were similar to the RESPONSE study. Baseline demographics and disease characteristics were comparable between the two treatment arms and similar to the patient population of the RESPONSE study. The primary endpoint was the proportion of patients achieving HCT control (absence of phlebotomy eligibility) at Week 28. The key secondary endpoint was the proportion of patients achieving complete hematological remission at Week 28.

RESPONSE-2 met its primary objective with a higher proportion of patients in the Jakavi arm (62.2%) compared to the BAT arm (18.7%) achieving the primary endpoint ( $p<0.0001$ ). The key secondary endpoint was also met with significantly more patients achieving a complete hematologic remission in the Jakavi arm (23.0%) compared to the BAT arm (5.3%;  $p=0.0019$ ). At week 28, the proportion of patients achieving a  $\geq 50\%$  reduction in symptom burden as measured by the MPN-SAF total symptom score was 45.3% in the Jakavi arm and 22.7% in the BAT arm.

#### **Graft-versus-host disease**

Two randomized phase 3, open-label, multi-center studies investigated Jakavi in patients 12 years of age and older with acute GvHD (REACH2) and chronic GvHD (REACH3) after allogeneic hematopoietic stem cell transplantation (alloSCT) and insufficient response to corticosteroids and other systemic therapies. The starting dose of Jakavi was 10 mg twice daily.

#### **Acute graft-versus-host disease**

In REACH2, 309 patients with Grade II to IV corticosteroid-refractory, acute GvHD were randomized 1:1 to Jakavi or BAT. Patients were stratified by severity of acute GvHD at the time of randomization. Corticosteroid refractoriness was determined when patients had progression after at least 3 days, failed to achieve a response after 7 days or failed corticosteroid taper.

BAT was selected by the investigator on a patient-by-patient basis and included anti-thymocyte globulin (ATG), extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab.

In addition to Jakavi or BAT, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medications and transfusion support as well as standard acute GvHD prophylaxis and treatment medications initiated before randomization including systemic corticosteroids and calcineurin inhibitors (CNIs) such as cyclosporine or tacrolimus. Topical or inhaled corticosteroid therapies were allowed to be continued per institutional guidelines.

Patients randomized to the BAT arm were allowed to cross over to the Jakavi arm after the Day 28 visit. Tapering of Jakavi was allowed after the Day 56 visit for patients with treatment response.

Baseline demographics and disease characteristics were balanced between the two treatment arms. The median age was 54 years (range 12 to 73 years). The study included 2.9% adolescent, 59.2% male and 68.9% white patients. The majority of enrolled patients had malignant underlying disease.

The severity of acute GvHD was Grade II in 34% and 34%, Grade III in 46% and 47%, and Grade IV in 20% and 19% of the Jakavi and BAT arms, respectively.

The reasons for patients' insufficient response to corticosteroids in the Jakavi and BAT arm were i) failure in achieving a response after 7 days of corticosteroid treatment (46.8% and 40.6%, respectively), ii) failure of corticosteroid taper (30.5% and 31.6%, respectively) or iii) disease progression after 3 days of treatment (22.7% and 27.7%, respectively).

Among all patients, the most common organs involved in GvHD were skin (54.0%) and lower GI tract (68.3%). More patients in the Jakavi arm had acute GvHD involving skin (60.4%) and liver (23.4%), compared to the BAT arm (skin: 47.7% and liver: 16.1%).

The most frequently used prior systemic acute GvHD therapies were corticosteroids+CNIs (49.4% in the Jakavi arm and 49% in the BAT arm).

The primary endpoint was the overall response rate (ORR) on Day 28, defined as the proportion of patients in each arm with a complete response (CR) or a partial response (PR) without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response based on investigator assessment following the criteria by Harris et al (2016).

The key secondary endpoint was the proportion of patients who achieved an ORR at Day 28 and maintained it at Day 56.

A further secondary endpoint was Failure Free Survival (FFS), a composite time to event endpoint defined as the time from randomization to i) relapse or recurrence of underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy.

REACH2 met its primary objective. ORR at Day 28 of treatment was higher in the Jakavi arm (62.3%) compared to the BAT arm (39.4%). There was a statistically significant difference between the treatment arms (stratified Cochrane-Mantel-Haenszel test  $p<0.0001$ , one-sided, OR: 2.64; 95% CI: 1.65, 4.22).

There was also a higher proportion of complete responders in the Jakavi arm (34.4%) compared to BAT arm (19.4%).

Day-28 ORR was 76% for Grade II GvHD, 56% for Grade III GvHD, and 53% for Grade IV GvHD in the Jakavi arm, and 51% for Grade II GvHD, 38% for Grade III GvHD, and 23% for Grade IV GvHD in the BAT arm.

Among the non-responders at Day 28 in the Jakavi and BAT arms, 2.6% and 8.4% had disease progression, respectively.

Overall results are presented in Table 9.

**Table 9      Overall response rate at Day 28 in REACH2**

	Jakavi		BAT	
	N = 154		N = 155	
	n (%)	95% CI	n (%)	95% CI
Overall Response	96 (62.3)	54.2, 70.0	61 (39.4)	31.6, 47.5
OR (95% CI)		2.64 (1.65,4.22)		
p-value		p <0.0001		
Complete Response		53 (34.4)		30 (19.4)
Partial Response		43 (27.9)		31 (20.0)

The study met its key secondary endpoint. Durable ORR at Day 56 was 39.6% (95% CI: 31.8, 47.8) in the Jakavi arm and 21.9% (95% CI: 15.7, 29.3) in the BAT arm. There was a statistically significant difference between the two treatment arms (OR: 2.38; 95% CI: 1.43, 3.94; p=0.0005). The proportion of patients with a CR was 26.6% in the Jakavi arm vs. 16.1% in the BAT arm. Overall, 49 patients originally randomized to the BAT arm crossed over to the Jakavi arm.

For the secondary endpoint FFS there were fewer events in the Jakavi arm (91; 59.1%) than in the BAT arm (121; 78.1%). Among the randomized patients, the estimated incidence rate of a FFS event at one month was lower in the Jakavi arm (17.92%; 95% CI: 12.26, 24.46) than in the BAT arm (49.13%; 95% CI: 40.94, 56.80). Additional follow-up data remain in favor of Jakavi. Median FFS with Jakavi was statistically significantly longer than with BAT (4.86 months vs. 1.02 months; HR: 0.49, 95% CI: 0.37, 0.63; p<0.0001)

#### **Chronic graft-versus-host disease**

In REACH3, 329 patients with moderate or severe corticosteroid-refractory, chronic GvHD were randomized 1:1 to Jakavi or BAT. Patients were stratified by severity of chronic GvHD at the time of randomization. Corticosteroid refractoriness was determined when patients had lack of response or disease progression after 7 days, or had disease persistence for 4 weeks or failed corticosteroid taper twice.

BAT was selected by the investigator on a patient-by-patient basis and included extracorporeal photopheresis (ECP), low dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, or ibrutinib.

In addition to Jakavi or BAT, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medications and transfusion support as well as standard chronic GvHD prophylaxis and treatment medications initiated before randomization including systemic corticosteroids and CNIs (cyclosporine or tacrolimus). Topical or inhaled corticosteroid therapy was allowed to be continued per institutional guidelines.

Patients randomized to the BAT arm were allowed to cross over to the Jakavi arm after the Cycle 7 Day 1 visit (week 24). Tapering of Jakavi was allowed after the Cycle 7 Day 1 visit.

Baseline demographics and disease characteristics were balanced between the two treatment arms. The median age was 49 years (range 12 to 76 years). The study included 3.6% adolescent, 61.1% male and 75.4% white patients. The majority of enrolled patients had malignant underlying disease.

The severity at diagnosis of corticosteroid-refractory chronic GvHD was balanced between the two treatment arms, with 41% and 45% moderate, and 59% and 55% severe, in the Jakavi and the BAT arms, respectively.

Patients' insufficient response to corticosteroids in the Jakavi and BAT arm were characterized by i) a lack of response or disease progression after corticosteroid treatment for at least 7 days at 1mg/kg/day of prednisone equivalents (37.6% and 44.5%, respectively), ii) disease persistence after 4 weeks at 0.5 mg/kg/day (35.2% and 25.6%), or iii) corticosteroid dependency (27.3% and 29.9%, respectively).

Among all patients, 73% and 45% had skin and lung involvement in the Jakavi arm, compared to 69% and 41% in the BAT arm.

The most frequently used prior systemic chronic GvHD therapies were corticosteroids only (43% in the Jakavi arm and 49% in the BAT arm) and corticosteroids+CNIs (41% patients in the Jakavi arm and 42% in the BAT arm).

The primary endpoint was the ORR on Day 1 of Cycle 7, defined as the proportion of patients in each arm with a CR or a PR without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response based on investigator assessment per NIH criteria.

Key secondary endpoints were Failure Free Survival (FFS) and proportion of patients with improvement of the modified Lee symptoms score (mLSS) at Cycle 7 Day 1. FFS, a composite time to event endpoint, incorporated the earliest of the following events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for chronic GvHD.

REACH3 met its primary objective. ORR at week 24 was higher in the Jakavi arm (49.7%) compared to the BAT arm (25.6%). There was a statistically significant difference between the treatment arms (stratified Cochrane-Mantel-Haenszel test  $p<0.0001$ , one-sided, OR: 2.99; 95% CI: 1.86, 4.80). Results are presented in Table 10

Among the non-responders at Cycle 7 Day 1 in the Jakavi and BAT arms, 2.4% and 12.8% had disease progression, respectively.

**Table 10      Overall response rate at Cycle 7 Day 1 in REACH3**

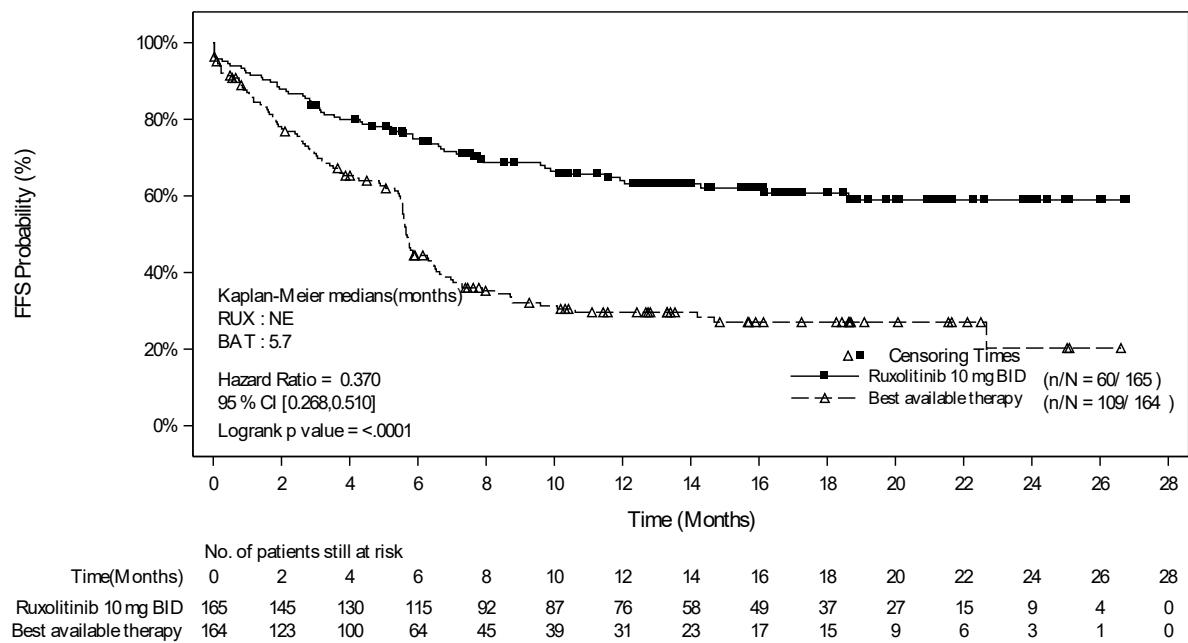
	Jakavi N = 165		BAT N = 164	
	n (%)	95% CI	n (%)	95% CI
Overall Response	82 (49.7)	41.8, 57.6	42 (25.6)	19.1, 33.0
OR (95% CI)	2.99 (1.86, 4.80)			
p-value	p < 0.0001			
Complete Response	11 (6.7)		5 (3.0)	
Partial Response	71 (43.0)		37 (22.6)	

Both key secondary endpoints were also met. FFS demonstrated a statistically significant superiority of Jakavi versus BAT (HR: 0.370; 95% CI: 0.268, 0.510) with a 63% decreased risk (See Figure 12-4). The 6-months FFS probability (95% CI) was 73.84 (66.4%, 79.88%) and 45.45% (37.46%, 53.08%) for the Jakavi and BAT arms, respectively. The majority of FFS events were ‘addition or initiation of another systemic therapy for cGvHD’. The 6-months probability for this event was 13.5% and 48.5% for the Jakavi and BAT arms, respectively.

The rate of responders as per improvement of  $\geq 7$  points of total symptom score (TSS) from baseline of the mLSS showed a statistically significant difference ( $p=0.0011$ ) between the Jakavi (24.2%) and BAT arms (9.8%).

Another secondary endpoint was best overall response (BOR) defined as the proportion of patients who achieved ORR (CR+PR) at any time point up to Cycle 7 Day 1. The BOR up to Cycle 7 Day 1 was higher in the Jakavi arm (76.4%) than in the BAT arm (60.4%).

The estimated probability of maintaining BOR at 12 months was higher in the Jakavi arm compared to the BAT arm (64.5% [95% CI: 58.9, 76.3] vs 40.3% [95% CI: 30.3, 50.2]).

**Figure 4****Kaplan-Meier estimate of Failure Free Survival**

### Non-clinical safety data

Ruxolitinib has been evaluated in safety pharmacology, repeat dose toxicity, genotoxicity, reproductive toxicity studies and a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinib in repeat dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound  $C_{max}$ ) at the non-adverse effect level in the dog and rat studies were 15.7-fold and 10.4 fold greater, respectively, than the maximum human recommended 25 mg twice daily dose. No effects were noted in an evaluation of the neuropharmacologic effects of ruxolitinib.

Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. Ruxolitinib was administered daily by oral gavage at doses from 1.5 to 75 mg/kg/day from days 7 (the human equivalent of a newborn) to 63 post-partum (pp), 15 mg/kg/day from days 14 (the human equivalent of 1 year of age) to 63 pp and 5, 15 and 60 mg/kg/day from days 21 (the human equivalent of 2 to 3 years of age) to 63 pp. Doses  $\geq$ 30 mg/kg/day (1,200 ng\*h/mL based on unbound AUC) resulted in fractures and early termination of the groups when treatment started on day 7 pp. Reduced bone growth was observed at doses  $\geq$ 5 mg/kg/day ( $\geq$ 150 ng\*h/mL based on unbound AUC) when treatment started on day 7 pp and at  $\geq$ 15 mg/kg/day ( $\geq$ 150 ng\*h/mL based on unbound AUC) when treatment started on day 14 pp or day 21 pp. Based on unbound AUC, fractures and reduced bone growth occurred at exposures 13- and 1.5- fold the exposure in adult patients at the maximum recommended dose of 25 mg b.i.d, respectively. The effects were generally more severe when administration was initiated

earlier in the postnatal period. Other than the effects on bone development, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

Reproductive toxicity data are quoted in section Pregnancy, lactation, females and males of reproductive potential. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model nor in a 2-year study in rats.

## Pharmaceutical information

## Incompatibilities

Not applicable

### Special precautions for storage

Do not store above 30°C.

The expiry date is indicated on the packaging.

Jakavi does not require any special storage condition.

Jakavi must be kept out of the reach and sight of children.

### Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements

### Pack size

Box, 1 blister @ 14 tablets

Jakavi® 5 mg Reg. No.: DKI1567509010A1

Jakavi® 15 mg Reg. No.: DKI1567509010B1

Jakavi® 20 mg Reg. No.: DKI1567509010C1

## HARUS DENGAN RESEP DOKTER

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Leaflet based on CDS version 3.2 (12-Jan-2021 New Ind GyHD) Renewal 2025

## Informasi Produk Untuk Pasien

# JAKAVI®(Ruxolitinib)

Tablet 5 mg, 15 mg, 20 mg

### **Baca dengan saksama seluruh informasi pada brosur ini sebelum meminum obat.**

Simpan brosur ini baik-baik. Anda mungkin membutuhkannya untuk dibaca kembali.

Jika Anda memiliki pertanyaan lebih lanjut, silakan tanyakan kepada dokter atau apoteker Anda.

Obat ini diresepkan hanya untuk Anda. Anda dilarang memberikannya pada orang lain ataupun digunakan untuk penyakit yang lain.

Bila Anda mengalami efek samping yang berat atau efek samping apapun yang tidak tertulis pada brosur ini, segera hubungi dokter atau apoteker Anda.

### **Apa itu Jakavi dan kegunaannya**

#### **Apa itu Jakavi**

Jakavi merupakan obat resep dan mengandung bahan aktif ruxolitinib sebagai fosfat.

#### **Apa kegunaan Jakavi**

Jakavi digunakan untuk mengobati pasien dewasa dengan mielofibrosis, suatu jenis kanker darah yang langka dengan beberapa gejala seperti demam, berkeringat di malam hari, nyeri tulang, dan kehilangan berat badan. Pembesaran limpa merupakan salah satu karakteristik dari penyakit mielofibrosis.

Jakavi juga digunakan untuk mengobati pasien dewasa dengan polisitemia vera yang intoleran atau tidak bisa dikontrol dengan hidroksiuropa. Polisitemia vera merupakan penyakit darah serius yang jarang dengan berbagai gejala antara lain gatal-gatal (*pruritus*), sakit kepala, masalah penglihatan, rasa nyeri seperti terbakar parah pada tangan atau kaki, dan penyumbatan pembuluh darah. Pembesaran limpa juga kadang terjadi pada pasien dengan polisitemia vera.

Jakavi juga digunakan untuk merawat pasien berusia 12 tahun ke atas dan orang dewasa dengan penyakit graft-versus-host (GvHD) akut dan kronis yang tidak memberikan respons yang memadai terhadap kortikosteroid atau terapi sistemik lainnya. Penyakit ini terjadi setelah transplantasi darah atau sumsum tulang dari donor yang sehat ke pasien dan disertai dengan berbagai gejala yang memengaruhi banyak organ.

Ada dua bentuk GvHD: bentuk awal yang disebut GvHD akut yang biasanya berkembang segera setelah transplantasi dan dapat memengaruhi kulit, hati, dan saluran pencernaan, dan bentuk yang disebut GvHD kronis, yang berkembang kemudian, sekitar tiga bulan setelah transplantasi. Ini sering menyebabkan gejala pada kulit, hati, mulut, paru-paru, saluran pencernaan, sistem neuromuskuler, atau saluran genitourinari. Pada kulit menyebabkan ruam

kering, gatal, yang timbul dan menyerupai kulit buaya. Mungkin juga ada rambut rontok, penurunan keringat, dan rambut beruban yang muncul lebih cepat (prematur). Kekeringan mulut adalah gejala umum. Ini dapat berlanjut menjadi kepekatan terhadap makanan, sehingga makanan pedas dan asam dapat terasa menyengat. Dapat juga terjadi kekeringan, iritasi dan kemerahan pada mata. Hampir semua organ dapat dipengaruhi oleh GvHD kronis.

### **Cara kerja Jakavi**

Mielofibrosis adalah kelainan pada sumsum tulang, yang mana sumsum tersebut digantikan dengan jaringan parut sehingga tidak lagi dapat memproduksi cukup sel darah normal dan mengakibatkan pembengkakan limpa secara signifikan. Jakavi dapat mengurangi ukuran limpa pada pasien dengan beberapa bentuk mielofibrosis dengan cara menghambat secara selektif enzim yang disebut *Janus Associated Kinase* (JAK1 dan JAK2) sehingga dapat meredakan gejala dan menurunkan risiko potensi komplikasi darah atau pembuluh darah yang serius.

Polisitemia vera merupakan kelainan pada sumsum tulang, di mana sumsum memproduksi terlalu banyak sel darah merah. Darah menjadi lebih kental dikarenakan peningkatan sel darah merah. Jakavi dapat meringankan gejala, mengurangi ukuran limpa dan volume sel darah merah yang diproduksi oleh pasien dengan polisitemia vera dengan secara selektif menghambat enzim yang dinamakan *Janus Associated Kinases* (JAK1 dan JAK2), sehingga secara potensial mampu mengurangi risiko komplikasi serius dari darah atau pembuluh darah.

Penyakit graft-versus-host adalah komplikasi yang terjadi setelah transplantasi ketika sel-sel tertentu (sel T) dalam cangkokan donor (misalnya sumsum tulang) tidak mengenali sel/organ inang dan menyerangnya. Dengan memblokir enzim secara selektif yang disebut *Janus Associated Kinases* (JAK1 dan JAK2), Jakavi efektif untuk mengurangi tanda dan gejala bentuk akut dan kronis dari penyakit cangkok versus inang yang mengarah pada perbaikan penyakit dan kelangsungan hidup sel yang ditransplantasikan.

Silakan tanyakan dokter Anda apabila Anda masih memiliki pertanyaan mengenai cara kerja Jakavi atau alasan obat ini diresepkan untuk Anda.

### **Apa yang perlu diketahui sebelum dan selama pengobatan dengan Jakavi?**

Ikuti baik-baik seluruh petunjuk dokter Anda meskipun mungkin saja berbeda dengan informasi umum yang terdapat pada brosur ini.

### **Jangan minum Jakavi**

- **Apabila Anda alergi** (hipersensitif) terhadap ruxolitinib, zat aktif dari Jakavi ataupun kandungan lainnya (lihat bagian akhir brosur). Apabila Anda merasakan adanya reaksi alergi, segera mintakan saran kepada dokter Anda.

Apabila hal ini sesuai dengan kondisi Anda, **beritahukan dokter sehingga Anda tidak perlu memulai pengobatan dengan Jakavi.**

## **Sebelum memulai pengobatan dengan Jakavi**

Beritahukan dokter bila:

- Anda mengalami infeksi
- Anda memiliki masalah pada ginjal
- Anda sedang atau pernah memiliki masalah pada liver
- Anda sedang meminum obat yang lain (lihat bagian Penggunaan Bersama Obat-obatan Lainnya)
- Anda pernah menderita tuberkulosis
- Anda pernah menderita kanker kulit
- Anda pernah menderita hepatitis B

## **Selama pengobatan dengan Jakavi**

Segera beritahukan dokter bila:

- Anda mengalami memar dan/atau perdarahan tiba-tiba, kelelahan yang tidak wajar, napas pendek saat berolahraga atau istirahat, tampak pucat, atau mengalami infeksi berulang yang cukup sering (tanda-tanda kelainan darah).
- Anda mengalami gejala-gejala adanya infeksi atau munculnya ruam kulit yang nyeri disertai gelembung kecil berair (tanda-tanda cacar ular).
- Anda mengalami batuk kronis dengan dahak berdarah, demam, berkeringat pada malam hari dan penurunan berat badan (ini merupakan tanda tuberkulosis).
- Anda mengalami gejala di bawah ini atau orang yang dekat dengan anda menyadari bahwa anda mengalami gejala berikut: kebingungan, kehilangan keseimbangan atau sulit berjalan, lindung, sulit bicara, penurunan kekuatan atau kelemahan pada salah satu sisi tubuh, pandangan kabur atau kehilangan penglihatan (ini merupakan gejala *progressive multifocal leukoencephalopathy*).
- Anda merasakan perubahan pada kulit. Hal ini butuh observasi lebih lanjut, karena beberapa tipe kanker kulit (non-melanoma) pernah dilaporkan.

## **Pemantauan selama pengobatan dengan Jakavi**

Sebelum memulai terapi, dokter akan meminta Anda untuk melakukan pemeriksaan darah untuk menentukan dosis awal yang tepat untuk Anda. Dokter Anda juga akan memeriksa apakah Anda memiliki tanda-tanda atau gejala infeksi sebelum memulai pengobatan dan selama pengobatan dengan Jakavi.

Selama menjalani pengobatan dengan Jakavi Anda juga akan mendapatkan beberapa pemeriksaan untuk memantau jumlah sel darah di dalam tubuh Anda (seperti sel darah putih, sel darah merah, dan trombosit) untuk melihat respon tubuh Anda terhadap pengobatan yang diberikan atau apabila Jakavi memberikan efek tidak diinginkan terhadap sel-sel tersebut sehingga dokter perlu untuk menyesuaikan kembali dosis Jakavi yang diberikan ataupun menghentikannya. Dokter Anda mungkin juga akan melakukan pengecekan rutin terhadap kadar lemak darah Anda.

## **Penggunaan bersama obat-obatan lainnya**

Anda umumnya dapat melanjutkan penggunaan obat-obatan lainnya selama meminum Jakavi. Namun, lebih baik tetap beritahukan dokter atau apoteker Anda apabila Anda sedang meminum atau baru-baru ini mendapatkan pengobatan dengan obat-obatan lain, termasuk obat-obatan yang Anda beli tanpa resep dokter.

Hal ini penting khususnya untuk obat-obatan di bawah ini karena dokter mungkin saja perlu untuk menyesuaikan pemberian dosis Jakavi untuk Anda.

- Beberapa obat untuk pengobatan infeksi, termasuk obat anti jamur (obat anti jamur seperti tapi tidak terbatas pada obat berikut ini: ketokonazole, itrakonazole, fluconazole dan vorikonazole) atau obat antibakteri (antibiotik seperti tapi tidak terbatas pada obat berikut ini: klaritomisin, atau telitromisin), atau obat antivirus termasuk tapi tidak terbatas pada obat AIDS berikut ini: (*atazanavir, indinavir, nelfinavir, ritonavir, saquinavir*).
- *Nefazodone*, obat untuk depresi.

**Selama meminum Jakavi** Anda tidak boleh memulai minum obat apapun tanpa memberitahukan terlebih dahulu dokter yang meresepkan Jakavi untuk Anda. Hal ini berlaku baik untuk golongan obat-obatan resep, obat bebas dan bebas terbatas, dan obat-obatan herbal atau alternatif.

## **Penggunaan bersamaan dengan makanan atau minuman**

Anda harus meminum Jakavi setiap hari pada saat yang sama, baik secara bersamaan ataupun tidak bersamaan dengan makanan.

### **Pasien usia lanjut (65 tahun ke atas)**

Tidak ada persyaratan khusus untuk pasien dengan usia 65 tahun ke atas.

### **Pasien anak-anak dan remaja (di bawah 18 tahun)**

Jakavi tidak boleh digunakan untuk anak-anak ataupun remaja, yang memiliki penyakit mielofibrosis atau polisitemia vera. Untuk pengobatan penyakit graft-versus-host, Jakavi dapat digunakan pada pasien berusia 12 tahun ke atas.

## **Penggunaan selama kehamilan dan menyusui**

Minta saran dari dokter atau apoteker Anda sebelum meminum obat-obatan apapun.

- Dokter akan memberikan beberapa saran untuk menghindari kehamilan selama Anda mendapatkan pengobatan dengan Jakavi.
- Jakavi tidak direkomendasikan untuk digunakan selama kehamilan. Bila Anda sedang hamil atau merasa mungkin hamil, sangat penting untuk memberitahukannya kepada dokter sehingga dokter dapat mendiskusikan dengan Anda mengenai kemungkinan Anda mendapatkan Jakavi selama kehamilan Anda.
- Anda tidak diperbolehkan menyusui anak Anda selama mendapatkan pengobatan dengan Jakavi. Belum diketahui apakah Jakavi dapat masuk ke dalam air susu Ibu.

## **Bagaimana cara menggunakan Jakavi?**

Ikuti instruksi dokter dengan saksama. Jangan meminum Jakavi lebih dari yang diresepkan dokter untuk Anda.

## **Berapa banyak Jakavi yang perlu diminum**

Dokter akan memberitahukan Anda dengan tepat berapa banyak tablet Jakavi yang perlu Anda minum.

Untuk menentukan dan mempertahankan dosis Jakavi yang sesuai untuk Anda, dokter terlebih dahulu akan memeriksa sel-sel darah dan kondisi liver dan ginjal Anda. Dokter juga perlu mengetahui bila Anda sedang dalam pengobatan dengan obat-obatan tertentu, pastikan Anda memberitahukan dokter Anda apabila Anda sedang menggunakan obat-obatan lainnya.

Bila Anda mengalami efek samping tertentu yang disebabkan oleh Jakavi (misalnya kelainan darah), dokter mungkin perlu menyesuaikan jumlah Jakavi yang Anda minum atau meminta Anda untuk menghentikan Jakavi untuk sementara.

Jangan menghentikan penggunaan Jakavi terkecuali atas petunjuk dokter Anda.

## **Kapan perlu meminum Jakavi**

Minum Jakavi dua kali sehari, setiap hari, di waktu yang kurang lebih sama setiap harinya. Meminum Jakavi di waktu yang sama setiap hari sangat penting untuk mempertahankan kadar obat di dalam darah.

Bila Anda sedang mendapatkan tindakan pencucian darah (dialisis), minum 1 tablet Jakavi sebelum dan 1 tablet lagi sesudah dialisis. Dokter akan memberitahukan dosis tablet yang Anda perlukan untuk diminum sebelum dan sesudah proses dialisis.

## **Bagaimana cara meminum Jakavi**

Tablet Jakavi adalah untuk diminum melalui mulut, baik bersamaan ataupun tanpa makanan.

Telan seluruh tablet bersama dengan segelas air.

## **Berapa lama perlu meminum Jakavi**

Anda harus melanjutkan meminum Jakavi selama waktu yang diberitahukan oleh dokter Anda. Pengobatan ini adalah pengobatan jangka panjang. Dokter akan memantau kondisi Anda secara rutin untuk memastikan Anda memperoleh manfaat dari pengobatan ini.

Apabila Anda masih memiliki pertanyaan mengenai berapa lama waktu yang Anda perlukan untuk meminum obat ini, bicarakan dengan dokter ataupun apoteker Anda.

## **Apabila Anda meminum Jakavi melebihi dosis yang seharusnya**

Bila Anda secara tidak sengaja meminum Jakavi melebihi dosis yang diresepkan untuk Anda, segera hubungi dokter, perawat, ataupun apoteker yang melayani Anda.

### **Apabila Anda lupa meminum Jakavi**

Jangan minum Jakavi dengan dosis yang digandakan untuk mengganti dosis yang terlewatkan tersebut. Bila Anda lupa untuk meminum Jakavi, tetap minum dosis berikutnya sesuai dengan jadwal yang telah ditetapkan.

### **Apabila Anda berhenti meminum Jakavi**

Apabila Anda menghentikan pengobatan dengan Jakavi begitu saja, gejala-gejala terkait mielofibrosis dan polisitemia vera yang pernah Anda alami sebelumnya mungkin saja kembali. Pada GvHD, pengurangan dosis atau penghentian Jakavi dimungkinkan jika Anda menanggapi pengobatan dan dokter Anda akan mengawasi prosedur ini. Oleh sebab itu, Anda tidak diperbolehkan menghentikan pengobatan Jakavi dan tidak merubah dosis tanpa mengkonsultasikannya dengan dokter terlebih dahulu.

Apabila Anda masih memiliki pertanyaan terkait penggunaan produk ini, silakan tanyakan kepada dokter ataupun apoteker Anda.

### **Efek samping yang mungkin timbul**

Sama halnya dengan obat-obatan lainnya, pasien yang mendapatkan pengobatan Jakavi dapat mengalami efek samping, walaupun tidak setiap orang pasti mendapatkannya.

Kebanyakan efek samping bersifat ringan hingga sedang dan umumnya hilang setelah beberapa hari hingga beberapa minggu pengobatan.

### **Mielofibrosis (MF)**

Efek samping berikut telah dilaporkan terkait dengan pengobatan Jakavi pada pasien dewasa.

Beberapa efek samping bisa serius

Segara cari bantuan medis sebelum mengambil dosis terjadwal berikutnya jika Anda mengalami efek samping serius berikut ini:

**Sangat umum:** dapat memengaruhi lebih dari 1 dari 10 orang

- Demam, batuk, sulit atau nyeri bernapas, mengi, nyeri dada saat bernapas (kemungkinan gejala pneumonia)
- Kelelahan, lemas, kulit pucat (kemungkinan gejala anemia yang disebabkan oleh rendahnya kadar sel darah merah), sering infeksi, demam, menggigil, sakit tenggorokan atau sariawan akibat infeksi (kemungkinan gejala neutropenia yang disebabkan oleh rendahnya tingkat sel darah putih), perdarahan atau memar spontan (kemungkinan gejala trombositopenia yang disebabkan oleh rendahnya kadar trombosit)
- Demam, nyeri saat buang air kecil sebagai tanda infeksi saluran kemih (urinary tract infection)
- Ruam lepuhan kecil berisi cairan, muncul pada kulit yang memerah, tanda herpes zoster (herpes zoster)

**Umum:** dapat memengaruhi hingga 1 dari setiap 10 orang

- Jumlah ketiga jenis sel darah yang rendah - sel darah merah, sel darah putih, dan trombosit (pansitopenia)

**Jarang:** dapat memengaruhi hingga 1 dari setiap 100 orang

- Batuk kronis dengan dahak bercampur darah, demam, keringat malam, dan penurunan berat badan (gejala tuberkulosis)

#### **Efek samping lainnya**

Kemungkinan efek samping lainnya termasuk yang tercantum di bawah ini. Jika efek samping ini memberat, beri tahu dokter, apoteker, atau penyedia layanan kesehatan Anda.

**Efek samping sangat umum:** dapat memengaruhi lebih dari 1 pada 10 pasien

- Memar
- Kadar tinggi pada kolesterol (hiperkolesterolemia) atau lemak pada darah (hipertrigliceridemia)
- Kenaikan berat badan
- Pusing
- Sakit kepala
- Konstipasi (susah buang air besar)
- Hasil pemeriksaan abnormal pada fungsi liver
- Tekanan darah tinggi (hipertensi) yang juga bisa menyebabkan pusing dan sakit kepala

**Efek samping umum:** dapat memengaruhi hingga 1 dari setiap 10 orang

- Peningkatan gas berlebihan di dalam perut (flatulen)

#### **Polisitemia vera (PV)**

Efek samping berikut telah dilaporkan terkait dengan pengobatan Jakavi pada pasien dewasa

#### **Beberapa efek samping bisa serius**

**Segera cari bantuan medis sebelum mengambil dosis terjadwal berikutnya jika Anda mengalami efek samping serius berikut ini:**

**Sangat umum:** dapat memengaruhi lebih dari 1 dari 10 orang

- Kelelahan, lemas, kulit pucat (kemungkinan gejala anemia yang disebabkan oleh rendahnya kadar sel darah merah), perdarahan spontan atau memar (kemungkinan gejala trombositopenia yang disebabkan oleh rendahnya kadar trombosit)

- Demam, nyeri saat buang air kecil sebagai tanda infeksi saluran kemih
- Ruam lepuhan kecil berisi cairan, muncul pada kulit yang memerah, tanda herpes zoster (herpes zoster)

**Umum:** *dapat memengaruhi hingga 1 dari setiap 10 orang*

- Demam, batuk, sulit atau nyeri bernapas, mengi, nyeri dada saat bernapas (kemungkinan gejala pneumonia)
- Sering mengalami infeksi, demam, menggigil, sakit tenggorokan atau sariawan akibat infeksi (kemungkinan gejala neutropenia yang disebabkan oleh rendahnya kadar sel darah putih)
- Jumlah ketiga jenis sel darah yang rendah - sel darah merah, sel darah putih, dan trombosit (pansitopenia)

**Tidak diketahui** (frekuensi tidak dapat diperkirakan):

- Batuk kronis dengan dahak bercampur darah, demam, keringat malam, dan penurunan berat badan (gejala tuberkulosis)

**Efek samping lainnya**

Kemungkinan efek samping lainnya termasuk yang tercantum di bawah ini. Jika efek samping ini menjadi parah, beri tahu dokter, apoteker, atau penyedia layanan kesehatan Anda.

**Efek samping sangat umum:** *dapat memengaruhi lebih dari 1 pada 10 pasien*

- Memar
- Kadar tinggi pada kolesterol (hiperkolesterolemia) atau lemak pada darah (hipertrigliceridemia)
- Pusing
- Kenaikan berat badan
- Sakit kepala
- Konstipasi (susah buang air besar)
- Hasil pemeriksaan abnormal pada fungsi liver
- Tekanan darah tinggi (hipertensi) yang juga bisa menyebabkan pusing dan sakit kepala

**Efek samping umum:** *dapat memengaruhi hingga 1 dari setiap 10 orang*

- Peningkatan gas berlebihan di dalam perut (flatulen)

**Penyakit graft-versus-host (GvHD)**

Efek samping berikut telah dilaporkan terkait dengan pengobatan Jakavi pada pasien berusia 12 tahun ke atas

## Beberapa efek samping bisa serius

**Segara cari bantuan medis sebelum mengambil dosis terjadwal berikutnya jika Anda mengalami efek samping serius berikut ini:**

**Sangat umum:** dapat memengaruhi lebih dari 1 dari 10 orang

- Demam, nyeri, kemerahan, dan/atau kesulitan bernapas sebagai tanda infeksi sitomegalovirus (infeksi sitomegalovirus)
- Demam, nyeri saat buang air kecil sebagai tanda infeksi saluran kemih
- Detak jantung cepat, demam, bingung dan napas cepat sebagai tanda kondisi serius yang terjadi sebagai respons terhadap infeksi yang menyebabkan peradangan luas (sepsis)
- Kelelahan, lemas, kulit pucat (kemungkinan gejala anemia yang disebabkan oleh rendahnya kadar sel darah merah), sering infeksi, demam, menggigil, sakit tenggorokan atau sariawan akibat infeksi (kemungkinan gejala neutropenia yang disebabkan oleh rendahnya tingkat sel darah putih), perdarahan atau memar spontan (kemungkinan gejala trombositopenia yang disebabkan oleh rendahnya kadar trombosit)
- Jumlah ketiga jenis sel darah yang rendah - sel darah merah, sel darah putih, dan trombosit (pansitopenia)

## Efek samping lainnya

Kemungkinan efek samping lainnya termasuk yang tercantum di bawah ini. Jika efek samping ini menjadi parah, beri tahu dokter, apoteker, atau penyedia layanan kesehatan Anda.

**Sangat umum:** dapat memengaruhi lebih dari 1 dari 10 orang

- Kolesterol tinggi (hiperkolesterolemia)
- Sakit kepala
- Tekanan darah tinggi (hipertensi)
- Merasa sakit perut (mual)
- Hasil tes fungsi hati abnormal
- Peningkatan kadar enzim dalam darah dari otot yang berpotensi menunjukkan kerusakan otot dan/atau kerusakan otot (peningkatan kreatin fosfokinase darah)
- Peningkatan kadar kreatinin dalam darah, suatu zat yang biasanya dikeluarkan oleh ginjal ke dalam urin, yang mungkin berarti ginjal Anda tidak berfungsi dengan baik (peningkatan kreatinin darah)

**Umum:** dapat memengaruhi hingga 1 dari setiap 10 orang

- Demam, nyeri, kemerahan, dan/atau kesulitan bernapas sebagai tanda infeksi virus BK (infeksi virus BK)
- Berat badan
- Sembelit

Bila Anda mengalami salah satu dari efek samping tersebut di atas, beritahukan dokter Anda.

Bila Anda juga menemukan efek samping apapun yang tidak tercakup dalam brosur ini, harap juga beritahukan pada dokter atau apoteker yang melayani Anda.

### **Pelaporan efek samping**

Apabila ada keluhan efek samping atau kondisi tidak nyaman selama dan setelah penggunaan obat, konsultasikan ke dokter, apoteker, atau perawat. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut:

Novartis Indonesia

Website: [www.novartis.com/report](http://www.novartis.com/report)

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

### **Bagaimana cara menyimpan Jakavi?**

- Jangan minum Jakavi setelah melewati batas kadaluarsa yang tertera pada dusnya.
- Jangan simpan melebihi suhu 30°C.
- Simpan dalam kemasan aslinya.
- Jauhkan dari jangkauan dan penglihatan anak-anak.

Ikuti aturan dan persyaratan lokal mengenai prosedur pembuangan obat yang tidak terpakai.

### **Informasi lanjutan**

#### **Apa kandungan Jakavi**

Bahan aktif dari Jakavi adalah ruxolitinib.

Setiap tablet Jakavi 5 mg mengandung 5 mg ruxolitinib

Setiap tablet Jakavi 15 mg mengandung 15 mg ruxolitinib

Setiap tablet Jakavi 20 mg mengandung 20 mg ruxolitinib

Kandungan lainnya adalah selulosa mikrokristalin, magnesium stearat, silikon dioksida koloid, sodium starch glikolat, povidon, hidroksipropil selulosa, laktosa monohidrat.

Setiap 5 mg tablet Jakavi mengandung 71.45 mg laktosa monohidrat.

Setiap 15 mg tablet Jakavi mengandung 214.35 mg laktosa monohidrat.

Setiap 20 mg tablet Jakavi mengandung 285.80 mg laktosa monohidrat.

#### **Bagaimana rupa Jakavi dan berapa isi kemasannya**

Jakavi dipasarkan dalam bentuk tablet.

Tablet 5 mg berbentuk bulat dan berwarna putih.

Tablet 15 mg berbentuk oval dan berwarna putih.

Tablet 20 mg berbentuk seperti kapsul (kaplet) dan berwarna putih.  
Jakavi tersedia dalam kemasan Dus, 1 blister @ 14 tablet.

#### **HARUS DENGAN RESEP DOKTER**

Nomor Ijin Edar:

Jakavi® 5 mg Reg. No. DKI1567509010A1

Jakavi® 15 mg Reg. No. DKI1567509010B1

Jakavi® 20 mg Reg. No. DKI1567509010C1

#### **Produsen obat**

Dibuat oleh Novartis Pharma Stein AG, Stein, Switzerland.

Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

Apabila Anda masih memiliki pertanyaan mengenai obat ini, silakan hubungi dokter atau apoteker Anda.

*Based on BPL version 3.2 (12-Jan-2021\_Ind GvHD) **Renewal 2025***