NOVARTIS

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

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

Polycythemia vera

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

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 15 mg given orally twice daily for patients with a platelet count between 100,000 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3.

The recommended starting dose of Jakavi in Polycythemia vera (PV) is 10 mg given orally twice daily.

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and 100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be interrupted for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3.

In polycythemia vera, 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 should be considered if the platelet counts decrease below 100,000/ mm^3 with the goal of avoiding dose interruptions for thrombocytopenia. In polycythemia vera, dose reduction should also be considered if hemoglobin decreases below 12 g/dL and is recommended if hemoglobin decreases below 10 g/dL.

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-week intervals.

Administration instruction

The maximum dose of Jakavi is 25 mg twice daily.

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

Treatment may be continued as long as the benefit:risk remains positive.

Dose adjustment with concomitant strong CYP3A4 Inhibitors or fluconazole:

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Avoid the concomitant use of Jakavi with fluconazole doses of greater than 200 mg daily (see section Interactions).

More frequent monitoring (e.g. twice a week) of hematology parameters and clinical signs and symptoms of Jakavi related adverse reactions 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 count for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV 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^3 and 200,000/mm^3. 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^3. 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 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 patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. 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.

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

Safety and efficacy of Jakavi in pediatric patients have not been established.

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^3 or absolute neutrophil count less than 500/mm^3.

It has been observed that patients with low platelet counts (<200,000/mm^3) 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 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 haemotology paramaters 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^3) 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 these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to ruxolitinib 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 patients. Subsequent doses for both MF and PV 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 patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product (see section Dosage regimen and administration and Clinical pharmacology, Special populations).

Interactions

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), 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 randomised 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 three most frequent non-haematological ADRs were bruising (33.3%), dizziness (21.9%) and urinary track infections (21.4%).

The three most frequent non-haematological laboratory abnormalities were raised ALT (40.7%), raised AST (31.5%) and hypertriglyceridemia (25.2%). However, no CTCAE grade 3 or 4 hypertriglyceridemia and raised AST or grade 4 raised 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%) and thrombocytopenia (25.0%). Anaemia or thrombocytopenia Grade 3 and 4 were reported in respectively 2.9% or 2.6% of the patients, respectively.

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

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

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

Tabulated summary of adverse drug reactions from clinical trials

ADRs from clinical trials (Table 1) are listed by MedDRA system organ class (SOC). Within each SOC, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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.

Table 1 ADRs reported in the phase 3 studies COMFORT-I, COMFORT-II, RESPONSE, RESPONSE-2

Adverse drug reactions and CTCAE Grade[4]	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
Infections and infestations		
Urinary Tract infections[1,]	Very common	Very common
Herpes zoster[1]	Very common	Very common
Pneumonia[1]	Very common	Common
Tuberculosis*	Uncommon	-
Blood and lymphatic system disorders		
Bruising[1]	Very common	Very common
Anemia[2]		
CTCAE [1] Grade 4 (<6.5g/dL)	Very common	Uncommon
CTCAE Grade 3 (<8.0 to 6.5g/dL)	Very common	Common
Any CTCAE Grade	Very common	Very common
Thrombocytopenia[2]		
CTCAE Grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE Grade 3 (50,000 to 25,000/mm^3)	Very common	Common
Any CTCAE Grade	Very common	Very common
Neutropenia[2]		
CTCAE Grade 4 (<500/mm^3)	Common	Uncommon
CTCAE Grade 3 (<1000 to 500/mm^3)	Common	Uncommon
Any CTCAE Grade	Very common	Common
Pancytopenia[2.3]	Common	Common

Adverse drug reactions and CTCAE Grade[4]	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
Metabolism and nutrition disorders		
Hypercholesterolaemia [2] Any CTCAE Grade 1 and 2	Very common	Very common
Hypertriglyceridaemia[2] CTCAE Grade 1	-	Very common
Weight gain[1]	Very common	Very common
Nervous system disorders		
Dizziness[1]	Very common	Very common
Headache[1]	Very common	-
Gastrointestinal disorders		
Constipation[1]	-	Very Common
Flatulence[1]	Common	-
Hepatobiliary disorders		
Raised ALT[2] CTCAE Grade 3 (> 5x to 20 x ULN)	Common	Common
Any CTCAE Grade	Very common	Very common
Raised AST[2] Any CTCAE Grade	Very common	Very common
Vascular disorders		
Hypertension[1]	Very common	Very common

[1] Frequency is based on AE data.

[2] Frequency is based on laboratory values.

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

[4] CTCAE Version 3.0;

Grade 1=mild, Grade 2= moderate, Grade 3=severe, Grade 4=life-threatening or disabling.

ULN = upper limit of normal

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.

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%

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^3 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^3 to 200,000/mm^3 before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (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.

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.

Urinary tract infections

In the randomised 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.

Over the randomized period in the RESPONSE and RESPONSE-2 studies in PV, one (0.5%) Grade 3 to 4 urinary tract infection was observed.

During the long term follow-up, urinary tract infection of any grade was observed in 21.4% and 11.8% of MF and PV patients, respectively.

Herpes zoster

The rate of herpes zoster was similar in PV (4.3%) patients and MF patients (4.0%). There was one report of Grade 3 and 4 post herpetic neuralgia amongst the PV patients.

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.

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%.

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 foses 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 levonorgestred. 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_{50} 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_{50}'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-α, IL-6) and resulted in significantly prolonged survival in the mice at doses that did not cause myelosuppressive effects.

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 TNFalpha, 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 decrease 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_{max}) 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 insufficiency

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 insufficiency

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 patients with hepatic impairment (see section Dosage regimen and administration).

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 X 10^9/L) and circulating blasts ≥1%. The starting dose of Jakavi was based on platelet count. Patients with a platelet count between 100,000 and 200,000/mm^3 were started on Jakavi 15 mg twice daily and patients with a platelet count >200,000/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^3, and 190 (63.1%) had a baseline platelet count >200,000/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 ≤125,000/mm^3, of 10 mg twice daily for patients with platelet counts between 75,000 to ≤100,000/mm^3, and of 5 mg twice daily for patients with platelet counts between 50,000 to ≤75,000/mm^3.

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 ≥35% reduction from baseline in spleen volume at Week 24 as measured by MRI or CT.

Secondary endpoints included duration of maintenance of a ≥35% reduction from baseline in spleen volume, proportion of patients who had a ≥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 ≥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 ≥35% reduction of spleen volume measured by MRI or CT from baseline to Week 24. Duration of maintenance of a ≥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^3. 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 2. A significantly larger proportion of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline in both studies compared to placebo in COMFORT-I and BAT in COMFORT-II.

Table 2 Percent of Patients with ≥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 ≥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 ≥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 ≥50% reduction in palpable spleen length.

In COMFORT-II, 28.5% of patients in the Jakavi arm achieved a ≥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 ≥35% reduction of spleen volume at Week 24. A significantly larger proportion of patients in the Jakavi arm 46 patients (31.9%) achieved a ≥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 ≥ 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**

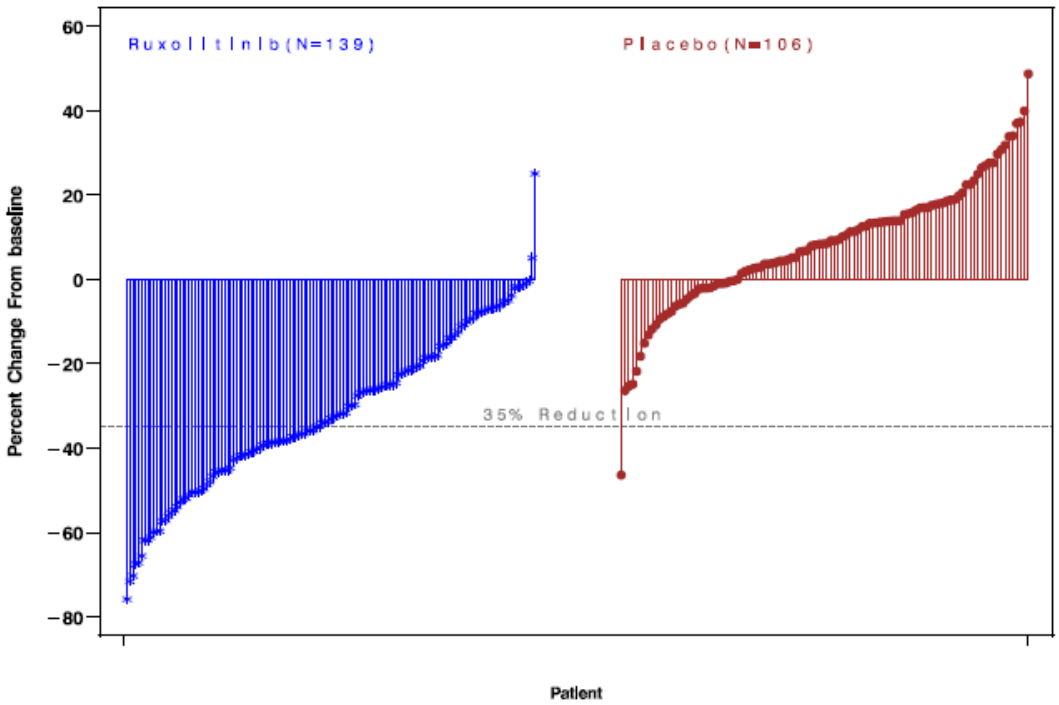
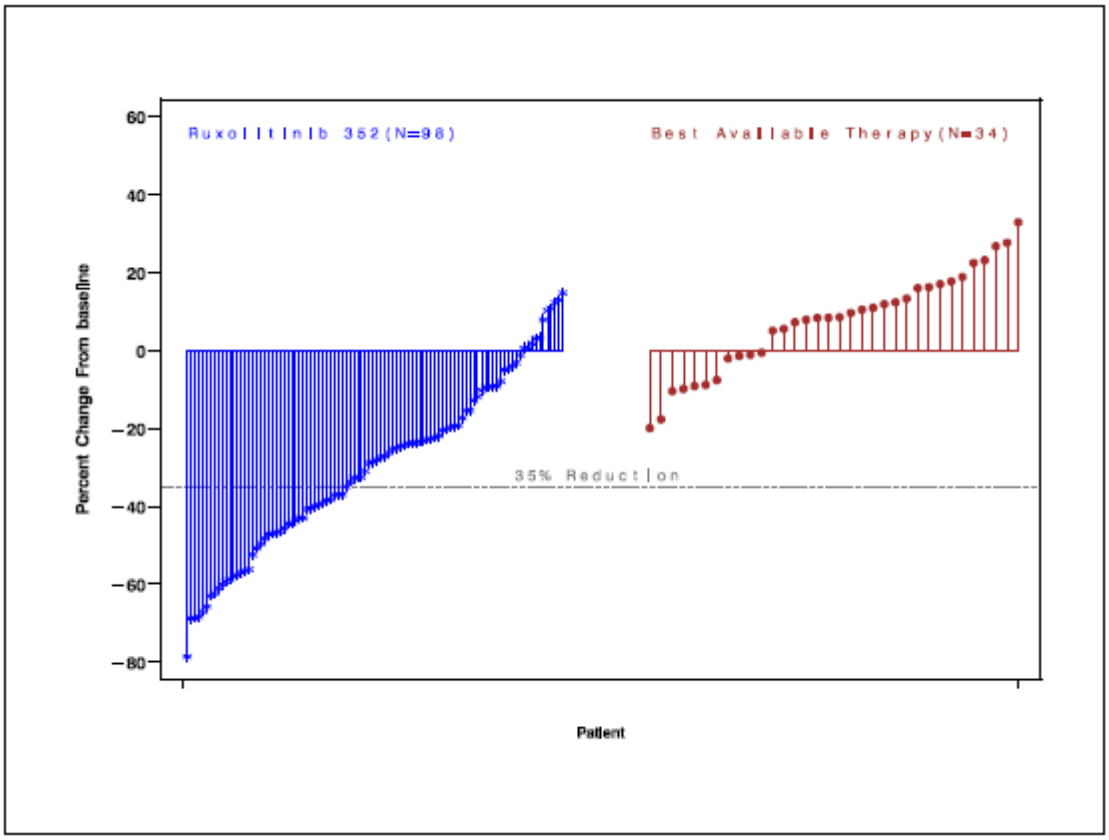


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the Jakavi arm who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was 28%. Among the 34 patients in the BAT 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 ≥35% reduction of spleen volume to 25% increase from nadir and loss of response in COMFORT-I and COMFORT-II is shown in Table 3.

Table 3 **Kaplan-Meier Analysis of Duration from 1st ≥ 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 ≥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 ≥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%).

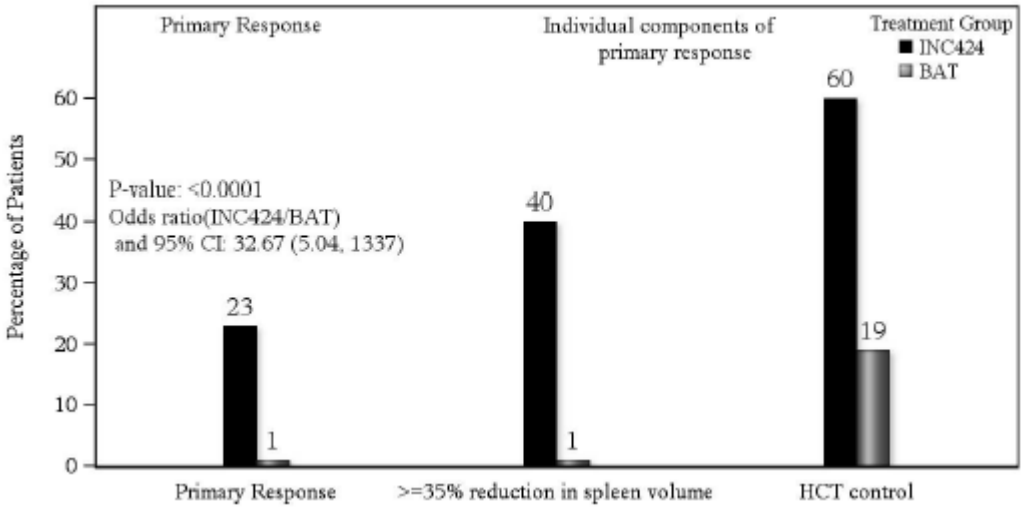
Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the Jakavi arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most 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 ≥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 ≥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 ≥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 4)

Table 4 **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 ≥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 ≥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.

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 ≥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 ≥5 mg/kg/day (≥150 ng*h/mL based on unbound AUC) when treatment started on day 7 pp and at ≥15 mg/kg/day (≥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

Box, 4 blisters @ 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 3.1 (26-Oct-2020 safety related changes)

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 kegunaan Jakavi dan bagaimana cara kerjanya

Kegunaan Jakavi

Jakavi merupakan obat resep yang digunakan untuk mengobati pasien dewasa dengan *myelofibrosis*, 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 *myelofibrosis*.

Jakavi juga digunakan untuk mengobati pasien dengan *polycythemia vera* yang intoleran atau tidak bisa dikontrol dengan hidroksiurea. *Polycythemia 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 *polycythemia vera*.

Cara kerja Jakavi

Jakavi mengandung zat aktif yang disebut ruxolitinib.

Myelofibrosis 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 *myelofibrosis* 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.

DISETUJUI OLEH BPOM: 24/08/2021 ID REG: EREG10000512100031 - EREG10000512100036

Polycythemia vera merupakan kelainan pada sumsum tulang, dimana 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 *polycythemia vera* dengan secara selektif menghambat enzim yang dinamakan *Janus Associated Kinases* (JAK1 dan JAK2), sehingga secara potensial mampu mengurangi resiko komplikasi serius dari darah atau pembuluh darah.

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

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.

Sebelum meminum Jakavi

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

Jangan minum Jakavi

- **Apabila Anda alergi** (hipersensitif) terhadap ruxolitinib, ataupun kandungan lainnya pada Jakavi (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 tuberculosis
- 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 berair (tanda-tanda cacar air).
- Anda mengalami batuk kronis dengan dahak berdarah, demam, berkeringat pada malam hari dan penurunan berat badan (ini merupakan tanda *tuberculosis*).
- Anda mengalami gejala di bawah ini atau orang yang dekat dengan anda menyadari bahwa anda mengalami gejala berikut: kebingungan, kehilangan keseimbangan atau sulit berjalan, kecerobohan, sulit bicara, penurunan kekuatan atau kelemahan pada salah satu sisi tubuh, pandangan kabur atau kehilangan penglihatan (ini merupakan gejala *progressive multifocal leukoencephalopaty).*
- Anda merasakan perubahan pada kulit. Hal ini butuh observasi lebih lanjut, karena beberapa tipe kanker kulit (non-melanoma) pernah dilaporkan.

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.

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 meminum 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 pengunaan 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 *myelofibrosis* yang pernah Anda alami sebelumnya mungkin saja kembali. Oleh sebab itu, Anda tidak diperbolehkan menghentikan pengobatan Jakavi 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.

Myelofibrosis (MF)

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

- Infeksi saluran kemih
- Cacar air (*herpes zoster*)
- Demam, batuk, sesak napas, mengi, kesulitan atau nyeri saat bernapas (kemungkinan gejala pneumonia)
- Kelelahan, kulit pucat (yang mungkin merupakan gejala anemia yang disebabkan oleh kadar rendah pada sel darah merah), infeksi, demam, menggigil, radang tenggorokan atau sariawan karena infeksi (yang mungkin merupakan gejala neutropenia yang disebabkan kadar rendah pada sel darah putih), pendarahan spontan atau memar (yang mungkin merupakan gejala trombositopenia yang disebabkan kadar rendah pada trombosit).
- Memar
- Kadar tinggi pada kolesterol (hiperkolesterolemia) atau lemak pada darah (hipertrigliseridemia)
- 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 antara 1-10 pada setiap 100 pasien*

- Rendahnya kadar dari ketiga sel darah – sel darah merah, sel darah putih dan trombosit (yang disebut juga dengan pansitopenia)
- Peningkatan gas berlebihan di dalam perut (flatulen)
-

Efek samping jarang: *dapat memengaruhi antara 1-10 pada setiap 1000 pasien*

- Batuk kronis dengan dahak berdarah, demam, berkeringat pada malam hari dan penurunan berat badan (gejala tuberculosis)

Polycythemia Vera (PV)

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

- Kelelahan, kulit pucat (yang mungkin merupakan gejala anemia yang disebabkan oleh kadar rendah pada sel darah merah), pendarahan spontan atau memar (yang mungkin merupakan gejala trombositopenia yang disebabkan kadar rendah pada trombosit).
- Infeksi saluran kemih

- Cacar air (*herpes zoster*)
- Memar
- Kadar tinggi pada kolesterol (hiperkolesterolemia) atau lemak pada darah (hipertrigliseridemia)
- 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 antara 1-10 pada setiap 100 pasien*

- Demam, batuk, sesak napas, mengi, kesulitan atau nyeri saat bernapas (kemungkinan gejala pneumonia)
- Infeksi, demam, menggigil, radang tenggorokan atau sariawan karena infeksi (yang mungkin merupakan gejala neutropenia yang disebabkan kadar rendah pada sel darah putih)
- Rendahnya kadar dari ketiga sel darah – sel darah merah, sel darah putih dan trombosit (yang disebut juga dengan pansitopenia)
- Peningkatan gas berlebihan di dalam perut (flatulen)

Efek samping jarang: *dapat memengaruhi antara 1-10 pada setiap 1000 pasien*

- Batuk kronis dengan dahak berdarah, demam, berkeringat pada malam hari dan penurunan berat badan (gejala tuberculosis)

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.

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, natrium 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 dan Dus, 4 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 3.1 (26-Oct-2020 safety related changes)