NOVARTIS

Jakavi®

Protein kinase inhibitors.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

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

10 mg tablets: round curved white to almost white tablets with 'NVR' debossed on one side and 'L10' 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

Ruxolitinib phosphate

Ruxolitinib 5 mg per tablet

Ruxolitinib 10 mg per tablet

Ruxolitinib 15 mg per tablet

Ruxolitinib 20 mg per tablet.

Active Moiety

Ruxolitinib.

Certain dosage strengths may not be available in all countries.

Excipients

Cellulose, microcrystalline, Magnesium stearate, Silica, colloidal anhydrous,

Sodium starch glycolate (Type A), Hydroxypropylcellulose, Povidone

Each 5 mg tablet contains 71.45 mg of lactose monohydrate

Each 10 mg tablet contains 142.90 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 disease-related splenomegaly and/or symptoms in adult patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Polycythemia vera

Jakavi is indicated for the treatment of adult patients with polycythemia vera 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 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 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.

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 moderate 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 INTERACTION).

More frequent monitoring of hematology parameters and clinical signs and symptoms of Jakavi related adverse reactions is recommended while on a strong CYP3A4 inhibitor or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes.

Special populations

Renal impairment

In patients with severe renal impairment (creatinine clearance (Clcr) less than 30mL/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50%. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients diagnosed with severe renal impairment while receiving Jakavi should be carefully monitored and may need to have their doses reduced to avoid adverse drug reactions.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on dialysis. Available data in this population suggest that MF patients on dialysis should be started on an initial single dose of 15 mg or 20 mg based on platelet counts with subsequent single doses only after each dialysis session, and with careful monitoring of safety and efficacy. 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. 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 (see section CLINICAL PHARMACOLOGY).

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 stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

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 reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with Jakavi (for monitoring frequency see section DOSAGE REGIMEN AND ADMINISTRATION).

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.

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 initiate appropriate treatment promptly. Jakavi therapy should not be started until active serious infections have resolved.

Tuberculosis has been reported in patients receiving Jakavi for myelofibrosis. 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 and aspartate aminotransferase, 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 leukoencephalopathy

Progressive Multifocal leukoencephalopathy (PML) has been reported with ruxolitinib 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 end stage renal disease on dialysis the starting dose should be based on platelet counts for MF patients (myelofibrosis), while the recommended starting dose is a single dose of 10 mg for PV patients (polycythemia vera). Subsequent doses for both MF and PV patients should be administered only on hemodialysis days following each dialysis session. Further dose modifications should be based on the safety and efficacy of the drug (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY, Special populations).

Hepatic impairment

The starting dose of Jakavi should be reduced in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the drug (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special populations).

Interactions

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual moderate 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 (for monitoring frequency see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

The concurrent use of cytoreductive therapies or haematopoietic growth factors with Jakavi has not been studied. The safety and efficacy of these co-administrations are not known (see section INTERACTIONS)

Withdrawal effects

Following interruption or discontinuation of Jakavi, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, 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, although the utility of the tapering is unproven.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Safety assessment was based on a total of 982 patients (with myelofibrosis or polycythemia vera) receiving Jakavi in Phase 2 and 3 studies.

Myelofibrosis:

In the randomized period of the two pivotal studies COMFORT-I and COMFORT-II, patients had a median duration of exposure to Jakavi of 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of the 301 patients, 111 (36.9%) had a baseline platelet count between 100,000/mm^3 and 200,000/mm^3, and 190 (63.1%) had a baseline platelet count >200,000/mm^3.

In these clinical studies, discontinuation due to adverse events, regardless of causality was observed in 11.3% of patients.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia.

Hematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%).

Anemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.6%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%).

Long term safety data from two pivotal phase 3 studies assessing 457 patients with myelofibrosis treated with ruxolitinib, including data from patients initially randomized to ruxolitinib (n=301; exposure 0.3 to 68.1 months, median exposure 33.4 months) and patients who received ruxolitinib after crossing over from control treatments (n=156; exposure: 0.5 to 59.8 months, median exposure 25.0 months): The cumulative frequency of adverse events increased proportionally to the increase in the follow-up time.

With these updated data, therapy discontinuation due to adverse events was observed in 27.4% of patients treated with ruxolitinib.

Polycythemia vera

The safety of Jakavi was assessed in 184 patients with polycythemia vera in two open-label, randomized, controlled studies, the phase 3 RESPONSE study and the phase 3b RESPONSE-2 study. The adverse drug reactions listed below reflect the randomized study period (up to Week 32 for RESPONSE and up to week 28 for RESPONSE 2) with equivalent exposure to ruxolitinib and Best Available Therapy. The median duration of exposure to Jakavi during the

randomized study period was 7.85 months (range 0.03 to 7.85 months).

Discontinuation for adverse events, regardless of causality, was observed in 2.2% of patients.

Hematological adverse reactions (any CTCAE grade) included anemia (40.8%) and thrombocytopenia (16.8%). Anemia or thrombocytopenia Grade 3 and 4 were reported in respectively 1.1% or 3.3%.

The three most frequent non-haematologic adverse reactions were dizziness (9.2%), constipation (8.7%), and hypertension (6.5%).

The three most frequent non-haematological laboratory abnormalities (Any CTCAE grade) identified as adverse reactions were raised aspartate aminotransferase (26.1%), raised alanine aminotransferase (22.3%) and hypercholesterolaemia (20.7%). These were all Grade 1 to 2 with the exception of one Grade 3 raised alanine aminotransferase event.

Long term safety was evaluated using data from 367 patients with polycythemia vera treated with ruxolitinib in two phase 3 studies including data from patients initially randomized to ruxolitinib (n=184; exposure 0.03 to 43.5 months, median exposure 18.9 months) and patients who received ruxolitinib after crossing over from control treatments (n=149; exposure: 0.2 to 33.5 months, median exposure 12.0 months): With longer exposure, the cumulative frequency of AEs increased but no new safety findings emerged. When adjusted for exposure, the AE rates were generally comparable with those observed during the initial periods of the randomized studies.

Tabulated summary of adverse drug reactions from clinical studies

Adverse drug reactions from clinical studies (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: 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 study programme the severity of adverse drug reactions 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 Reports the frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE, RESPONSE 2)

Adverse drug reactions and CTCAE grade[3]	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary Tract infections[1]	Very common	Common
Pneumonia[1]	Common	-
Herpes zoster[1]	Common	Common
Tuberculosis[*]	Uncommon	-
Blood and lymphatic system disorders		
Anaemia[2]		
CTCAE [1] Grade 4 (<6.5g/dL)	Very common	Uncommon
CTCAE Grade 3 (<8.0 to 6.5g/dL)	Very common	Uncommon
Any CTCAE Grade	Very common	Very common

Thrombocytopenia[2]		
CTCAE Grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE Grade 3 (50,000 – 25,000/mm^3)	Common	Common
Any CTCAE Grade	Very common	Very common
Neutropenia[2]		
CTCAE Grade 4 (<500/mm^3)	Common	-
CTCAE Grade 3 (<1000 – 500/mm^3)	Common	-
Any CTCAE Grade	Very common	-
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding	Very common	Very common
Intracranial bleeding	Common	-
Gastrointestinal bleeding	Common	-
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Very common	Very common
Pancytopenia[2,3]	Common	-
Metabolism and nutrition disorders		
Weight gain[1]	Very common	Common
Hypercholesterolaemia [2] CTCAE Grade 1 and 2	Very common	Very common
Hypertriglyceridaemia [2] CTCAE Grade1	-	Very common
Nervous system disorders		
Dizziness[1]	Very common	Very common
Headache[1]	Very common	-
Gastrointestinal disorders		
Flatulence[1]	Common	-
Constipation[1]	-	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[2]		
CTCAE Grade 3 (> 5x – 20 x ULN)	Common	Uncommon
Any CTCAE Grade	Very common	Very common
Raised aspartate aminotransferase[2]		
Any CTCAE Grade	Very common	Very common
Skin and subcutaneous tissue disorders		
Bruising[1]	Very common	Very common
Vascular disorders		
Hypertension[1]	-	Common

[1] Frequency is based on adverse event 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 lab assessment

[4] Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0; Grade 1=mild, Grade 2= moderate, Grade 3=severe, Grade 4=life-threatening or disabling.

ULN = upper limit of normal

[*] Frequency is based on all patients exposed to ruxolitinib in clinical trials (N=4755)

Upon discontinuation, MF patients may experience a return of myelofibrosis symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In MF clinical studies the total symptom score for myelofibrosis symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section WARNINGS AND PRECAUTIONS).

In another experimental indication additional following ADRs have been observed: Hypertension (common), constipation (common), Hypertriglyceridemia CTCAE Grade 1 (very common).

Description of selected adverse drug reactions

Anaemia

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 anaemia.

In patients receiving Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomised, placebo-controlled study COMFORT-I 60.6% of Jakavi-treated patients and 37.7% of placebo-treated patients received red blood cell transfusions during randomized treatment. In the COMFORT-II study, the rate of packed red blood cell transfusions was 53.4% in the Jakavi arm and 41.1% in the best available therapy arm.

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 4.7% of patients receiving Jakavi and to 4.0% 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 38.5%).

Over the randomized period in the RESPONSE and RESPONSE 2, 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 clinical studies in MF, in patients who developed Grade 3 or 4 neutropenia, the median time to onset was 12 weeks. During the randomized period of the studies dose holding or reductions due to neutropenia were reported in 1.0% 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.

Bleeding

In the phase 3 MF pivotal studies bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to Jakavi and 23.2% of patients exposed to the reference treatments (placebo or best available therapy). The frequency of grade 3-4 events was similar for patients treated with Jakavi or reference treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%). Bruising events were more frequently reported in patients taking Jakavi compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to Jakavi and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to Jakavi compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

In the randomised period of the pivotal study in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 20% of patients treated with Jakavi and 15.3% patients receiving best available therapy. Bruising was reported in similar frequencies in Jakavi and BAT arms (10.9% versus 8.1%). No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving Jakavi. One patient treated with Jakavi experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage, gingival bleeding) were reported in 11.8% of patients treated with Jakavi and 6.3% treated with best available therapy.

Infections

In the phase 3 MF pivotal studies Grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%. Over the randomized period in the RESPONSE and RESPONSE-2 studies in PV, one (0.5%) Grade 3-4 urinary tract infection was observed.

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.

Increased systolic blood pressure

In the phase 3 MF pivotal clinical studies an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I the mean increase from baseline in systolic BP was 0-2 mmHg on Jakavi versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated patients.

INTERACTIONS

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus,

medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

Agents that may alter plasma concentration of ruxolitinib

Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)

In healthy subjects co-administration of Jakavi (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 33% and 91%, respectively, than with ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section DOSAGE REGIMEN AND ADMINISTRATION).

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). However, 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 400mg dose followed by 200mg 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. Avoid the concomitant use of Jakavi with fluconazole doses of greater than 200 mg daily.

CYP3A4 inducers (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum))

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section DOSAGE REGIMEN AND ADMINISTRATION).

In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near E_{max}. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

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 sytemic exposure of substrates of these transporters, such as dabigatran etixilate, 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 minimised if the time between administrations is kept apart as long as possible.

Other drug interactions studied

CYP3A4 substrates:

A study in healthy subjects indicated that Jakavi had no clinically significant pharmacokinetic interaction with midazolam (CYP3A4 substrate).

Oral contraceptives:

A 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 contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

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 (see section WARNINGS AND PRECAUTIONS).

Cytoreductive therapies

The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known (see section WARNINGS AND PRECAUTIONS).

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 25mg b.i.d based on AUC.

The use of Jakavi during pregnancy is not recommended. The patient should be advised of the risk to a 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 8% 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 passes into the milk of lactating rats. Because of the potential for serious adverse 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 in 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 males 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 Jakavi.

CLINICAL PHARMACOLOGY

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 STATs (signal transducers and activators of transcription) 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.

Myelofibrosis (MF) and Polycythemia vera (PV) are myeloproliferative neoplasms (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-alpha, 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 myelofibrosis 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 subjects with MF were decreased following treatment with ruxolitinib. Patients with myelofibrosis did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with polycythemia vera also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

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 pharmacokinetics 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 72 L in myelofibrosis patients with an inter-subject variability of 29.4% and 75 L in polycythemia vera 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 enzyme 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 total 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]-labeled 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 pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in myelofibrosis 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 myelofibrosis patients. Clearance was 12.7 L/h in polycythemia vera 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 ruxolitinib 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 end stage renal disease 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 end stage renal disease a modification of the dosing schedule is recommended (see section DOSAGE REGIMEN AND ADMINISTRATION).

Hepatic insufficiency

Following a single ruxolitinib 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 myelofibrosis (primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia-myelofibrosis). 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. Doses were then 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 ≥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 best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. In the best available therapy 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 primary myelofibrosis, 31% had post-polycythemia myelofibrosis and 18% had post-essential thrombocythemia myelofibrosis.

Twenty-one (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 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 subjects had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis, and 16% had post-essential thrombocythemia myelofibrosis. 19% of 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 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 below. 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 best available therapy 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)	Best Available Therapy (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 group achieved a ≥35% reduction in spleen volume from baseline compared with 0.7% in the placebo group at Week 24. A similar proportion of patients in the Jakavi group achieved a ≥50% reduction in palpable spleen length.

In COMFORT-II, 28.5% of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline compared with none (0%) in the best available therapy group 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 group 46 (31.9%) achieved a ≥35% reduction in spleen volume from baseline compared to no (0%) patients in the best available therapy group (p-value <0.0001).

A significantly higher proportion of patients in the Jakavi group achieved ≥ 35% reduction from baseline in spleen volume regardless of the presence or absence of the JAK2V617F

mutation or the disease subtype (primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis).

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 group 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 group 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

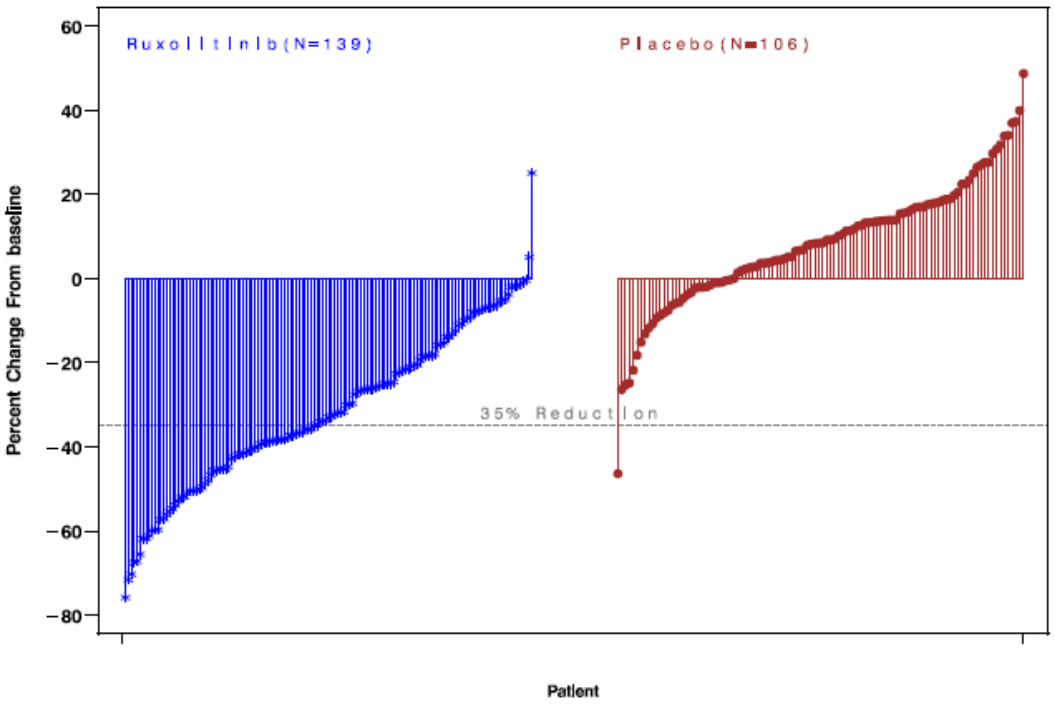
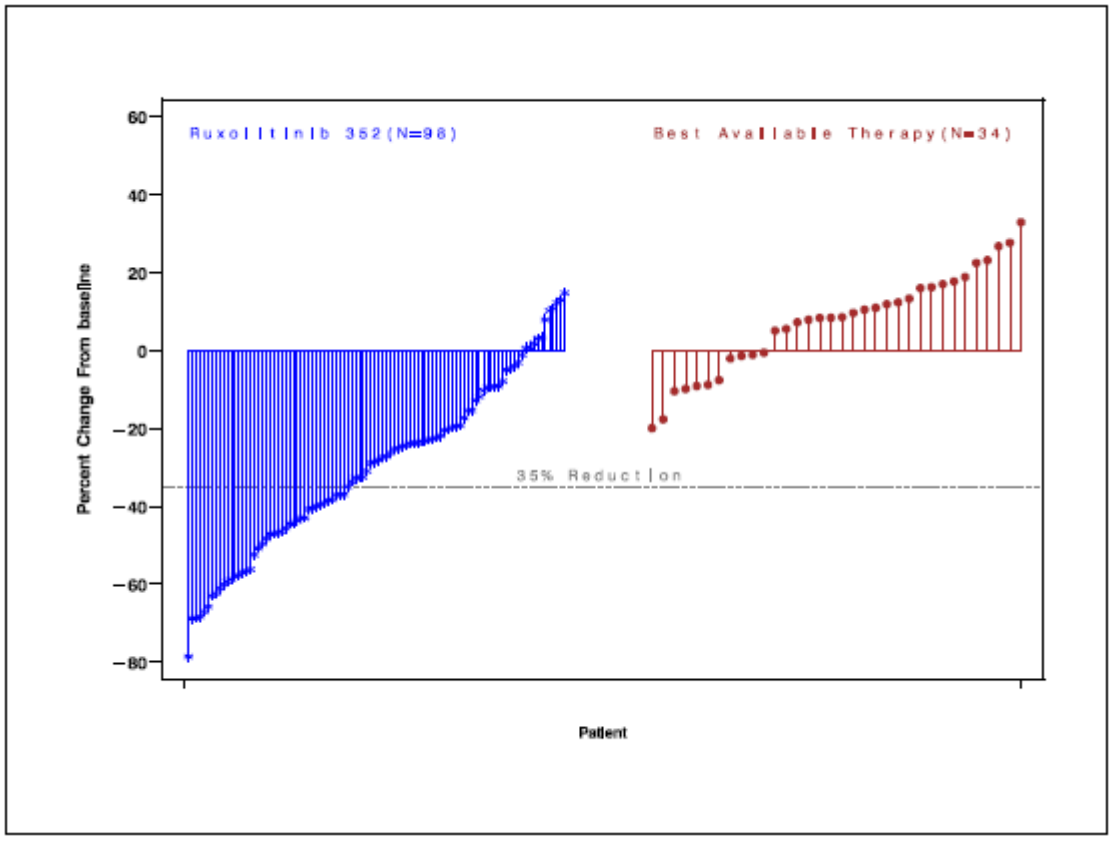


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the Jakavi group who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was 28%. Among the 34 patients in the Best Available Therapy group 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 below.

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 improves myelofibrosis-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 subjects completed daily. The change from Baseline in the Week 24 total score was a secondary endpoint in this study. Significantly larger proportion of subjects in the Jakavi group 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 EORTC QLQ-C30 in both COMFORT-I and COMFORT-II. COMFORT-I compared Jakavi to placebo at 24 weeks and COMFORT-II compared Jakavi to best available therapy at 48 weeks. At baseline for both studies, EORTC QLQ-C30 individual subscale scores for the Jakavi and comparator groups were similar. At Week 24 in COMFORT-I, the Jakavi group showed significant improvement in the global health status/quality of life of the EORTC QLQ-C30 compared with the placebo group (mean change of +12.3 and -3.4 for Jakavi and placebo, respectively, p <0.0001). At week 24 and week 48, the Jakavi group in COMFORT-II showed a trend towards greater improvement of global health status/quality of life compared to best available therapy, 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 ruxolitinib 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 ruxolitinib 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% Cl: 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 ruxolitinib was 19.9% (29 of 146 patients) versus 30.1% (22 of 73 patients) in patients randomized to best available therapy (BAT). There was a 52% reduction in risk of death in the ruxolitinib arm compared to BAT arm (HR 0.48; 95% CI 0.28-0.85; p= 0.009). At final analysis, after a median follow up of 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 polycythemia vera who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomized to the ruxolitinib 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 ruxolitinib 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. Comparative data regarding long-term survival and incidence of disease complications is missing.

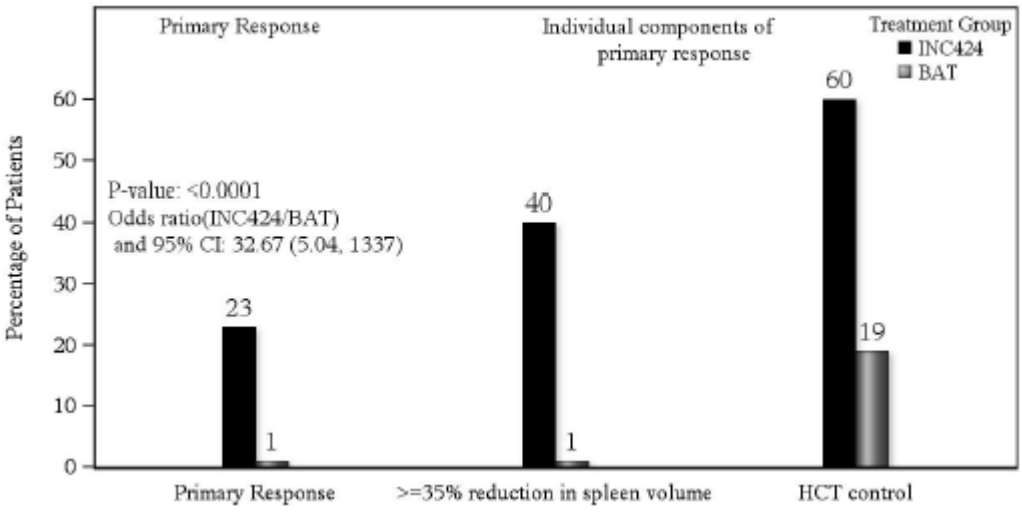
The primary composite endpoint was the proportion of patients achieving both the absence of phlebotomy eligibility (HCT control) and ≥ 35% reduction in spleen volume from baseline at Week 32. Phlebotomy eligibility was defined as a confirmed HCT > 45% that is at least 3 percentage points higher than 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 group 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). Hematocrit 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-SAF total symptom score (TSS) electronic patient diary consisting of 14 questions. At Week 32, 49% and 64% of patients treated with ruxolitinib 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. 66 % of ruxolitinib-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 ruxolitinib-treated patients at Week 32 (78% versus 33%).

Additional analyses from the RESPONSE study to assess durability of response were conducted at Week 80 only in the Jakavi arm. In this arm, 83% of patients were still on treatment at the time of the Week 80 data cut-off. Of patients who achieved a primary response at Week 32, 80% maintained their response for at least 48 weeks after the initial response. For patients who had achieved each of the components of the primary endpoint, all patients maintained spleen response and the probability of maintaining hematocrit

control for at least 80 weeks from the initial response was 89%. 69% of patients who achieved complete hematological remission at Week 32 maintained this response for at least 48 weeks.

A second randomized, open label, active-controlled phase IIIb study (RESPONSE-2) was conducted in 149 polycythemia vera patients who were resistant to or intolerant of hydroxyurea but without palpable splenomegaly. Seventy-four patients were randomized to the ruxolitinib 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, repeated dose toxicity, genotoxicity and reproductive toxicity studies and in a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinb in repeated 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 level in the dog and rat studies were 15.7-fold and 10.4-fold greater, respectively, than the maximum human recommended dose of 25 mg twice daily. No effects were noted in an evaluation of the neuropharmacological 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.

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration.

Reproductive toxicity data are quoted in PREGNANY, 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.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Jakavi should not be used after the date marked “EXP” on the pack.

Jakavi must be kept out of the reach and sight of

children. Store in original packaging.

Pack size

Blister pack of 14 tablets, 56 tablets

Not all pack sizes are marketed

Manufacturer:

See folding box.

International Package Leaflet

Information issued: May 2020.SIN

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