PRODUCT MONOGRAPH

Pr JAKAVI®

(ruxolitinib tablets)
(as ruxolitinib phosphate)

5 mg, 10 mg, 15 mg and 20 mg

Antineoplastic agent

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® Registered trademark

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(ruxolitinib tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 5 mg, 10 mg, 15 mg and 20 mg	Tablet content: Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

JAKAVI® is indicated for:

- the treatment of splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

- the control of hematocrit in adult patients with polycythemia vera (PV) resistant to or intolerant of a cytoreductive agent.

JAKAVI® should be initiated and monitored by a physician experienced in the use of antineoplastic therapies.

Geriatrics (> 65 years of age):
No additional dose adjustments are recommended for elderly patients.

Pediatrics (< 18 years of age):
Safety and efficacy of JAKAVI® in pediatric patients have not been established.

CONTRAINDICATIONS

Patients with known hypersensitivity to ruxolitinib or to any ingredient in the formulation of JAKAVI® or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

Patients who have or have had progressive multifocal leukoencephalopathy (PML) (see **WARNINGS AND PRECAUTIONS** section).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious bacterial, mycobacterial, fungal and viral infections including viral reactivation and other opportunistic infections (in some cases life-threatening or fatal) have been reported in patients treated with JAKAVI.

Reported infections included: Tuberculosis, Herpes Zoster, JC Virus and Hepatitis B.

Patients should be carefully assessed and monitored for the risk of developing serious infections. (see **WARNINGS and PRECAUTIONS, ADVERSE DRUG REACTIONS and Post-Marketing Adverse Drug Reactions** sections).

General

Interactions
If JAKAVI® is to be co-administered with strong CYP3A4 inhibitors or concomitant administration of moderate inhibitors of CYP3A4 and CYP2C9 (including a dual enzyme inhibitor as a single agent, e.g. fluconazole), the dose should be reduced to approximately 50% of the dose, rounding up to the nearest dosage strength. More frequent monitoring is recommended (see **DOSAGE AND ADMINISTRATION**, and **DRUG INTERACTIONS** sections).

Withdrawal effects in patients with myelofibrosis (MF)
Following interruption or discontinuation of JAKAVI, symptoms of myelofibrosis may return over a period of approximately 1 week. There have been cases of MF 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.

Carcinogenesis and Mutagenesis

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 JAKAVI has not been established. Patients should minimize exposure to

risk factors for skin cancer such as exposure to sunlight and other UV emitting sources while on JAKAVI. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Ruxolitinib was not carcinogenic in animal carcinogenic studies (see **TOXICOLOGY** section). Ruxolitinib did not test positive for mutagenicity or clastogenicity in the standard panel of genotoxicity assays (see **TOXICOLOGY** section).

Cardiovascular

Heart Rate Decrease and PR Interval Prolongation

JAKAVI causes a decrease in heart rate and a prolongation of the PR interval (see **WARNINGS AND PRECAUTIONS**, Monitoring and Laboratory Tests; **ADVERSE REACTIONS**, Electrocardiography sections). Caution should be observed in patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with JAKAVI (see **DRUG INTERACTIONS** section).

Lipid Abnormalities/ Elevations

Treatment with JAKAVI has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Lipid monitoring and treatment of dyslipidemia according to clinical guidelines is recommended (see **Monitoring and Laboratory Tests** section).

Hematologic

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 and during therapy (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests,** and **DOSAGE AND ADMINISTRATION** sections).

Patients with low platelet counts (<200,000/mm^3) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia is usually managed by reducing the dose or temporarily withholding JAKAVI. However, platelet transfusions may be required as clinically indicated (see **DOSAGE AND ADMINISTRATION**, and **ADVERSE DRUG REACTIONS** sections).

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) is managed by temporarily withholding JAKAVI (see **DOSAGE AND ADMINISTRATION**, and **ADVERSE DRUG REACTIONS** sections).

Hemorrhage

Bleeding (in some cases fatal) have been reported in patients treated with JAKAVI (see **ADVERSE DRUG REACTIONS** and **Post-Marketing Adverse Drug Reactions** sections). Platelet counts should be monitored.

Immune

Infections
Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections including pneumonia (in some cases fatal) have been reported in patients treated with JAKAVI.

Patients should be carefully assessed for the risk of developing serious bacterial, mycobacterial, fungal or viral infections. JAKAVI therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving JAKAVI for signs and symptoms of infections and initiate appropriate treatment promptly (see **ADVERSE DRUG REACTIONS, Post-Marketing Adverse Drug Reactions** and **TOXICOLOGY** sections).

The risk of visual disorders, including loss of vision, secondary to an eye infection may be a consequence of ruxolitinib-related infections. Physicians should carefully monitor patients receiving JAKAVI for eye infections in order to reduce the misdiagnosis of eye infections and to ensure patients receive the appropriate treatment.

Hepatitis B
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.

Tuberculosis
Tuberculosis, including fatal cases, has been reported in patients receiving JAKAVI for myelofibrosis. Before starting treatment, patients should be evaluated for active and inactive ('latent') tuberculosis (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory tests**). JAKAVI therapy should not be administered to patients with tuberculosis infection.

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 JAKAVI treatment. PML can cause severe disability and death. Relationship between the risk of PML and the JAKAVI treatment is not known. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if

such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. JAKAVI treatment should be withheld if PML is suspected and discontinued if PML is confirmed.

Special Populations

Renal impairment

The starting dose of JAKAVI should be reduced to approximately 50% of the recommended dose, rounding up to the nearest dosage strength for patients with moderate or severe renal impairment (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations** sections).

Patients with end-stage renal disease (ESRD) on hemodialysis require individualized dosing regimens. There are limited data to determine the best dosing options for these patients (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations** sections).

Further dose modifications should be based on the safety and efficacy of the drug (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations** sections).

Hepatic impairment

The starting dose of JAKAVI should be reduced to approximately 50% of the recommended dose, rounding up to the nearest dosage strength in patients with any degree of hepatic impairment. Further dose modifications should be based on the safety and efficacy of the drug (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations** sections).

Pregnant Women

There are no adequate and well-controlled studies of JAKAVI in pregnant women. Ruxolitinib was embryotoxic and fetotoxic in rats and rabbits (increases in post-implantation loss and reduced fetal weights) (see **TOXICOLOGY** section).

The potential risk of teratogenicity for humans is unknown. The use of JAKAVI during pregnancy should be avoided.

Nursing Women

Women taking JAKAVI should not breast-feed.

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. It is not known whether JAKAVI is excreted in human milk.

Women of childbearing potential

Women of child-bearing potential must take appropriate precautions to avoid becoming pregnant during treatment.

In case pregnancy occurs, risk/benefit evaluations must be carried out on an individual basis with careful counseling regarding potential risk to the fetus using the most recent data available.

Males
It is not known if ruxolitinib or its metabolites are present in semen. Male patients must take appropriate precautions to avoid fathering a child during JAKAVI treatment.

Fertility
There are no data on the effect of ruxolitinib on human fertility (see **TOXICOLOGY** section).

Sensitivity/Intolerance
JAKAVI contains lactose. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Geriatrics (> 65 years of age)
No additional dose adjustments are recommended for elderly patients.

Pediatrics (< 18 years of age)
Safety and efficacy of JAKAVI in pediatric patients have not been established.

Monitoring and Laboratory Tests

Blood cell counts: a blood cell count must be performed before initiating therapy with JAKAVI.

Complete blood counts should be monitored every 2-4 weeks until doses are stabilized, and then as clinically indicated (see **DOSAGE AND ADMINISTRATION** section).

Lipid monitoring: Lipid monitoring should be performed before initiating therapy with JAKAVI, then 4 weeks after starting therapy and regularly thereafter.

Liver and renal function tests: Liver and renal function tests should be performed prior to starting treatment with JAKAVI and periodically thereafter (see **DOSAGE AND ADMINISTRATION** section).

Cardiac Safety Monitoring: Patients receiving JAKAVI should be monitored for pulse rate and blood pressure. ECG evaluations should be performed at baseline and periodically during treatment with JAKAVI to monitor for decreased heart rate and PR interval prolongation (see **WARNINGS AND PRECAUTIONS**, Cardiovascular; **ADVERSE REACTIONS**, Electrocardiography; **DRUG INTERACTIONS** sections).

Tuberculosis test: A tuberculosis skin test and/or Interferon-gamma release assay should be performed before initiating therapy with JAKAVI to detect tuberculosis infection. However, these tests must be interpreted with caution in severely ill or immunocompromised patients given the possibility of a false negative result.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Patients with myelofibrosis:

For the primary safety analysis in patients with myelofibrosis, the median duration of exposure to JAKAVI was 10.8 months. The most frequently reported hematological adverse reactions (any CTCAE Grade; Common Terminology Criteria for Adverse Events, N=301 patients from ruxolitinib arms of COMFORT-I and COMFORT-II) included anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (15.6%). Anemia, thrombocytopenia and neutropenia are dose related effects.

The three most frequent non-hematological adverse reactions were bruising (21.3%), dizziness (15.0%) and headache (13.6%).

The three most frequent non-hematological laboratory abnormalities were raised alanine aminotransferase (26.9%), raised aspartate aminotransferase (19.3%) and hypercholesterolemia (16.6%).

In Phase III MF clinical studies, discontinuation due to adverse events, regardless of causality was observed in 10.0% of the JAKAVI-treated patients. The most common reason for discontinuation was thrombocytopenia in 0.7% of JAKAVI-treated patients. In the two phase III studies, 41.2% of the JAKAVI -treated patients had a dose reduction for thrombocytopenia.

In the randomized, placebo controlled study (COMFORT-I), 60.6% of JAKAVI-treated patients and 37.7% 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 53.4% in the JAKAVI arm and 41.1% in the best available therapy arm (BAT).

Long term safety data based on the 5 years follow-up from two pivotal phase III studies assessing 457 patients with myelofibrosis treated with JAKAVI during the randomized and extension periods included data from patients that were initially randomized to JAKAVI (n=301, duration of exposure: 0.3 to 68.1 months, median duration of exposure = 33 months) and patients that received JAKAVI after crossing over from control treatment arms (n=156, duration of exposure: 0.5 to 59.8 months, median duration of exposure = 25.0 months). The cumulative frequency of some adverse events was increased approximately proportionally to the increase in the follow-up time.

At the 5 year cut off, the most frequent hematological adverse reactions for patients randomized to and crossed-over to JAKAVI were anemia (all Grades 83.8%, ≥ Grade 3 48.6%), thrombocytopenia (all Grades 80.5%, ≥ Grade 3 22.5%) and neutropenia (all Grades 20.8%, ≥ Grade 3 9.8%).

The most frequent non-hematological adverse reactions, reported in the 5 years follow-up for patients randomized to and crossed-over to JAKAVI, were bruising (all Grades 33.3%, ≥ Grade 3 0.7%), Other bleeding events (all Grades 24.5%, ≥ Grade 3 4.2%), urinary tract infection (all Grades 21.2%, ≥ Grade 3 3.7%).

Overall, including the 5 years follow-up of the Phase III studies, discontinuation due to adverse events, regardless of causality was observed in 30.0% of the patients randomized to or crossed over to JAKAVI, the most frequently reported adverse events (preferred terms [PTs]) leading to study drug discontinuation were thrombocytopenia (2.6%); acute myeloid leukemia (2.0%) and anemia (1.5%).

Based on the 5 years follow-up, cumulatively, 17.5% patients died during treatment or within 28 days of treatment discontinuation. The most frequently reported causes of death by system organ class (SOC) included infections and infestations (4.8%), general disorders and administration site conditions (3.1%) patients, and cardiac disorders (2.2%).

Patients with polycythemia vera:

For the primary safety analysis in patients with polycythemia vera at week 32 for RESPONSE, the most frequently reported hematological adverse reactions (any CTCAE Grade, N=110 patients from JAKAVI arm of RESPONSE) included anemia (43.6%) and thrombocytopenia (24.5%).

The four most frequent non-hematologic adverse reactions reported at a higher frequency in the JAKAVI group than in the BAT group were diarrhea (14.5%), muscle spasm (11.8%), dizziness (11.8%) and dyspnea (10.0%) respectively.

The most frequent non-hematological laboratory abnormalities (any CTCAE Grade) in the JAKAVI group were hypercholesterolemia (30.0%), gamma glutamyl transferase (Hyper) (29.1%), bicarbonate (Hypo) (28.2%), lipase (Hyper) (28.2%), raised alanine aminotransferase (22.7%), glucose (Hypo) (22.7%), and raised aspartate aminotransferase (20.9%) respectively.

Discontinuation for adverse events, regardless of causality, was observed in 3.6% of patients treated with JAKAVI and 1.8% of patients treated with best available therapy. The most frequent adverse events leading to dose adjustment in the JAKAVI group were anemia and thrombocytopenia.

The long term 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 periods 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-hematological adverse reactions were dizziness (9.2%), constipation (8.7%), and hypertension (6.5%).

The three most frequent non-hematological 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.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Patients with Myelofibrosis:

At the time of the original marketing authorization application, JAKAVI has been administered to 617 patients with different disease settings. The safety profile of JAKAVI in patients with myelofibrosis was derived from 589 patients treated in two pivotal phase III studies and one phase II supporting study. In the clinical studies program, the severity of adverse drug reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 defining Grade 1=mild, Grade 2=moderate, Grade 3=severe and Grade 4=life-threatening or disabling.

At the time of the primary analysis for the randomized period of the two pivotal studies COMFORT-I and COMFORT-II, 301 patients had a median duration of exposure to JAKAVI of 10.8 months (range 2 weeks to 19.5 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.

COMFORT-I was a randomized, double-blind, placebo-controlled phase III study in patients with Primary Myelofibrosis (MF), Post-Polycythemia Vera Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-MF). Three hundred and nine (309) patients were randomized to this study. Patients were randomized to receive JAKAVI (155 patients) or matching placebo tablets (151 patients).

COMFORT-II was a randomized, open-label, efficacy and safety phase III study of JAKAVI tablets compared to best available therapy (BAT) in patients with PMF, PPV-MF or PET-MF. Two hundred and nineteen (219) patients were randomized to this study. Patients were stratified at baseline by prognostic risk category and randomized 2:1 to receive either JAKAVI (146 patients) or BAT (73 patients).

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions (ADRs) from clinical trials (Tables 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.

Table 1 Percentage of MF patients with adverse drug reactions ≥1% in clinical studies

System Organ Class/MedDRA Preferred term[1]	**COMFORT-I**				**COMFORT-II**			
	JAKAVI N=155		**Placebo N=151**		**JAKAVI N=146**		**Best available therapy N=73**	
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**
	All Grades	**≥ Grade 3**	**All Grades**	**≥ Grade 3**	**All Grades**	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Any ADR	64.5	6.5	38.4	5.3	56.8	11.0	32.9	5.6
Blood and lymphatic system disorders								
Any bleeding[2]	37.4	5.2	25.8	3.3	27.4	4.8	17.8	2.7
Bruising[3]	27.1	0.6	14.6	0	15.1	0	5.5	0
Other bleeding[4]	12.9	2.6	8.6	0.7	13.7	2.1	13.7	2.7
Gastrointestinal bleeding[5]	3.9	1.3	4.0	2.0	6.2	1.4	1.4	0
Intracranial bleeding[6]	0.6	0.6	1.3	1.3	1.4	1.4	0	0
Cardiac disorders								
Angina pectoris/ unstable angina	0	0	0	0	4.1	0	1.4	0
Bradycardia/ sinus bradycardia	3.2	0	1.3	0	3.4	0	0	0
Palpitation	2.6	0	0.7	0	4.8	0	1.4	0
Gastrointestinal disorders								
Flatulence	5.2	0	1.3	0	1.4	0	0	0
General disorders and administration site conditions								
Pyrexia	12.3	0.6	7.9	0.7	15.1	2.1	9.6	0
Infections and infestations								
Pneumonia	11.0	6.5	7.9	6.0	5.5	2.1	9.6	5.5
Urinary Tract infections[7]	9.7	0	5.3	1.3	15.1	2.1	6.8	0
Herpes zoster[8]	1.9	0	1.3	0.7	6.8	0.7	0	0
Tuberculosis	0	0	0	0	0.7	0.7	0	0
Metabolism and nutrition disorders								
Weight gain[9]	9.0	0.6	1.3	0.7	11.0	2.1	1.4	0.7
Nervous system disorders								

Dizziness[10]	19.4	0.6	7.9	0	10.3	0	9.6	2.7
Headache	15.5	0	6.0	0	11.6	1.4	5.5	0

- A subject with multiple occurrences of an ADR is counted only once in that ADR category.
- ADRs were counted at the most severe Grade.

[1]The frequency of most preferred terms displayed in this table is based on a group of similar preferred terms. These are annotated to each term.

[2] This includes all Preferred Terms noted below under 3, 4, 5 and 6.

[3] This includes the Preferred Terms of contusion, hematoma, ecchymosis, petechiae, increased tendency to bruise, periorbital hematoma, purpura, injection site hematoma and vessel puncture site hematoma.

[4]This includes the Preferred Terms of epistaxis, haematuria, post procedural hemorrhage, retinal hemorrhage, conjunctival hemorrhage, hemoptysis, disseminated intravascular coagulation, genital hemorrhage, hemorrhage, hemorrhagic anemia, intrabdominal hemorrhage, mouth hemorrhage, muscle hemorrhage, retroperitoneal hematoma, retroperitoneal hemorrhage, splenic hemorrhage, blood urine present, gingival bleeding, intra-abdominal haematoma, peritoneal hemorrhage, splenic haematoma.

[5] This includes the Preferred Terms of gastrointestinal hemorrhage, melaena, hemorrhoidal hemorrhage, rectal hemorrhage, hematochezia, oesophageal varices hemorrhage, upper gastrointestinal hemorrhage and gastric varices hemorrhage.

[6] This includes the Preferred Terms of cerebral hemorrhage and subdural hematoma.

[7] This includes the Preferred Terms of urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, pyuria, bacteria urine, kidney infection, bacteria urine identified and nitrite urine present.

[8] This includes the Preferred Terms of herpes zoster, postherpetic neuralgia, herpes virus infection and trigeminal neuralgia.

[9] This includes the Preferred Terms of weight increased and abnormal weight gain.

[10] This includes the Preferred Terms of dizziness, vertigo, balance disorder, dizziness postural and Meniere's. In addition a Grade 1 labyrinthitis was observed in 1 patient in Study 352 (JAKAVI arm).

Upon discontinuation, some patients have experienced a rapid return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies the total symptom score for MF symptoms gradually returned to baseline values within 7 days after dose discontinuation.

Description of selected adverse drug reactions

Infections

In phase III MF clinical studies, Grade 3 or 4 urinary tract infection was reported for 1.0% of patients, herpes zoster (any Grade) in 4.3% and tuberculosis (any Grade) in 1.0%. In addition, urosepsis was reported in 1.0% of patients and kidney infection was reported in 1 patient.

Bleeding

In the phase III pivotal MF 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 or 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 hemorrhage and haematuria) were reported in 13.3% of patients treated with JAKAVI and 10.3% treated with reference treatments.

Increased systolic blood pressure
In the phase III pivotal clinical MF 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 in the JAKAVI arm versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT II, mean values showed little difference between the JAKAVI treated and the control treated patients.

Electrocardiography
In the phase III MF clinical trials, steady-state treatment with JAKAVI was associated with statistically significant decreases from baseline in heart rate and statistically significant increases from baseline in the PR interval (see **WARNINGS AND PRECAUTIONS**, Cardiovascular & Monitoring and Laboratory Tests, **DRUG INTERACTIONS** sections). In the placebo-controlled trial, the placebo-adjusted mean changes from baseline in these parameters were statistically significant and ranged from -6 to -8 bpm for heart rate and 6 to 9 ms for the PR interval from weeks 4-24. Among subjects with normal PR values at baseline, the proportion who developed PR values >200 ms during treatment was 12.3% for JAKAVI, 4.9% for placebo, and 4.7% for best available therapy.

Statistically significant QTc prolongation was not observed in the placebo-controlled phase III trial. In the phase III trial versus best available therapy, statistically significant QTc increases from baseline of mean 4-5 ms were observed at weeks 4 and 24.

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 Hematology (laboratory data) in MF patients

Laboratory parameter	**COMFORT-I**				**COMFORT-II**			
	JAKAVI N=155		**Placebo N=151**		**JAKAVI N=146**		**Best available therapy N=73**	
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**
	All Grades	**≥ Grade 3**	**All Grades**	**≥ Grade 3**	**All Grades**	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Anemia	83.2	44.5	43.7	15.9	81.5	40.4	49.3	20.5
Thrombocytopenia	71.0	13.5	21.2	2.0	68.5	8.9	28.8	6.8
Neutropenia	18.7	7.1	4.0	3.3	12.3	6.2	8.2	1.4

Table 3 Biochemistry (laboratory data) in MF patients

Laboratory parameter	COMFORT-I				COMFORT-II			
	JAKAVI N=155		Placebo N=151		JAKAVI N=146		Best available therapy N=73	
	%	%	%	%	%	%	%	%
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Hepatobiliary disorders								
Raised alanine aminotransferase[1]	28.4	1.3	8.6	0	25.3	1.4	6.8	0
Raised aspartate aminotransferase	18.7	0	6.6	0	19.9	0	4.1	0
Metabolism and nutrition disorders								
Hypercholesterolemia	17.4	0	0.7	0	15.8	0	6.8	0

[1] In phase III clinical studies no CTCAE Grade 4 raised alanine aminotransferase was observed.

Anemia
In phase III 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 level reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually improved to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy. Female MF patients may be at higher risk of anemia than male MF patients.

Thrombocytopenia
In the Phase III 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 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 35.4%).

Neutropenia
In the phase III 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.

Patients with polycythemia vera:

At the time of the primary analysis the safety of JAKAVI was assessed in 240 patients with polycythemia vera treated with JAKAVI during a pivotal phase III study (n=206) and a supporting phase II study (n=34). The phase III study (RESPONSE study) was an open-label, randomized, controlled study. Patients were randomized to receive either 10 mg JAKAVI twice a day or Best Available Therapy (BAT). During the randomized period, 110 patients received JAKAVI and 111 patients received BAT. After 32 weeks of treatment, 96 patients from the BAT arm crossed-over to receive JAKAVI, which created an imbalance in drug exposure between the two arms. Consequently, the adverse drug reactions listed below are derived from the randomized study period (up to the week 32 visit) during which the exposures to JAKAVI and BAT were equivalent (median duration of exposure = 7.8 months in both arms). The mean age of patients was around 60 years.

Among patients randomized to JAKAVI, the median duration of exposure was 18.6 months (for the period up the cut-off date for the primary analysis of the pivotal study). An analysis of safety including data from the cross-over study period (median exposure 11.4 months) and a supportive phase II study (median exposure 48.1 months) was also performed. The cumulative frequency of AEs in JAKAVI-treated patients increased but no new safety findings emerged. When adjusted for exposure, the AE rates were generally comparable with those observed during the randomized study period.

Long term safety was evaluated using data from 367 patients with polycythemia vera treated with JAKAVI in two phase 3 studies (RESPONSE and RESPONSE 2) including data from patients initially randomized to JAKAVI (n=184; exposure 0.03 to 43.5 months, median exposure 18.9 months) and patients who received JAKAVI 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.

Tabulated summary of Adverse drug reactions from clinical trial

Table 4 Adverse drug reactions (≥3%) reported at a higher frequency (>1%) in the JAKAVI group than in the BAT group up to Week 32- in the RESPONSE study

System Organ Class/MedDRA Preferred Term	**JAKAVI N=110**		**Best available therapy N=111**	
	%	**%**	**%**	**%**
	All Grades	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Ear and labyrinth disorders				
Tinnitus	6 (5.5)	2 (1.8)	3 (2.7)	0 (0.0)

Gastrointestinal disorders				
Diarrhea	16 (14.5)	0 (0.0)	8 (7.2)	1 (0.9)
Constipation	9 (8.2)	0 (0.0)	3 (2.7)	0 (0.0)
Nausea	7 (6.4)	0 (0.0)	4 (3.6)	0 (0.0)
Infections and infestations				
Herpes zoster	7 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	5 (4.5)	1 (0.9)	0 (0.0)	0 (0.0)
Investigations				
Weight increased	6 (5.5)	0 (0.0)	1 (0.9)	0 (0.0)
Musculoskeletal and connective tissue disorders				
Muscle spasms	13 (11.8)	1 (0.9)	5 (4.5)	0 (0.0)
Back pain	6 (5.5)	1 (0.9)	4 (3.6)	0 (0.0)
Nervous system disorders				
Dizziness	13 (11.8)	0 (0.0)	11 (9.9)	0 (0.0)
Hypoaesthesia	4 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)
Psychiatric disorders				
Anxiety	4 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	11 (10.0)	3 (2.7)	2 (1.8)	0 (0.0)
Cough	9 (8.2)	0 (0.0)	6 (5.4)	0 (0.0)
Epistaxis	7 (6.4)	0 (0.0)	3 (2.7)	0 (0.0)
Oropharyngeal pain	4 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)
Vascular disorders				
Haematoma	6 (5.5)	0 (0.0)	3 (2.7)	0 (0.0)
Hypertension	5 (4.5)	1 (0.9)	3 (2.7)	1 (0.9)

- A subject with multiple occurrences of an ADR is counted only once in that ADR category.
- ADRs were counted at the most severe Grade

Table 5 Adverse drug reactions in patients with PV who received JAKAVI group or BAT group up to Week 28 in RESPONSE 2 study

Adverse drug reactions and CTCAE grade	**RESPONSE 2**	
	Ruxolitinib N=74	**BAT N=75**
	%	%
Infections and infestations		
Urinary tract infections[1]	6.8	0
Herpes zoster[1]	1.4	0
Blood and lymphatic system disorders		
Anemia[2]		
CTCAE[3] grade 4 (<6.5g/dL)	0	0
CTCAE grade 3 (<8.0–6.5g/dL)	0	0
Any CTCAE grade	36.5	21.3
Thrombocytopenia[2]		
CTCAE grade 4 (<25,000/mm^3)	0	1.3
CTCAE grade 3 (50,000 – 25,000/mm^3)	0	1.3
Any CTCAE grade	5.4	25.3
Metabolism and nutrition disorders		
Weight gain[1]	9.5	1.3
Hypercholesterolemia[2] Any CTCAE grade	6.8	0
Hypertriglyceridemia[2] Any CTCAE grade	9.5	1.3
Nervous system disorders		
Dizziness[1]	6.8	8.0
Gastrointestinal disorders		
Constipation[1]	9.5	5.3
Hepatobiliary disorders		
Raised alanine aminotransferase[2]		
CTCAE grade 3 (> 5x – 20 x ULN)	0	0
Any CTCAE grade	21.6	6.7

Raised aspartate aminotransferase[2] Any CTCAE grade	33.8	16.0
Vascular disorders		
Hypertension[1]	9.5	4.0
[1] Frequency is based on adverse event data. [2] Frequency is based on laboratory values. -A subject with multiple occurrences of an ADR is counted only once in that ADR category. -ADRs reported are on treatment or up to 28 days post treatment end date. [3] 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		

Description of selected adverse drug reactions

Infections

Over the randomized period in the pivotal Phase III study, one (0.9%) Grade 3-4 urinary tract infection was observed in PV patients. The rate of herpes zoster was higher in the JAKAVI arm (6.4%) than in BAT arm (0.0%). There was one report of Grade 3 and 4 post herpetic neuralgia amongst the PV patients.

At the most recent cut off, over the randomized period in the RESPONSE (32 weeks) and RESPONSE-2 (28 weeks) studies in PV, one (0.5%) Grade 3 to 4 urinary tract infection was observed. The rate of herpes zoster was reported in PV (4.3%) patients. There was one report of Grade 3 and 4 post herpetic neuralgia amongst the PV patients.

Electrocardiography

In the pivotal phase III PV study, at week 32, the mean change from baseline in heart rate was -5.84 vs +1.94 beat/min, in JAKAVI vs BAT arm respectively. Notably abnormal vital signs were comparable (< 5% difference) in both arms, except for low heart rate that was reported in 7.3% vs 1.8% of patients in JAKAVI vs BAT arm, respectively.

Abnormal Hematologic and Clinical Chemistry Findings

Table 6 Hematology (laboratory data) ≥2% in PV patients (up to week 32 in the RESPONSE Study)

	JAKAVI N=110		**BAT N=111**	
Laboratory parameter	**%**	**%**	**%**	**%**
	All Grades	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Anemia	43.6	1.8	30.6	0
Thrombocytopenia	24.5	5.4	18.9	3.6

Table 7 New or worsened biochemistry abnormalities in PV patients (at least 20% in all Grades of JAKAVI) up to week 32 by treatment group

	JAKAVI N=110		BAT N=111	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
Cholesterol (Hyper)	30.0	0	6.3	0
Gamma Glutamyl Transferase (Hyper)	29.1	3.6	21.6	3.6
Bicarbonate (Hypo)	28.2	0	30.6	0
Lipase (Hyper)	28.2	4.5	17.1	2.7
Alanine Aminotransferase (Hyper)	22.7	0.9	10.8	0
Glucose (Hypo)	22.7	0	22.5	0
Aspartate Aminotransferase (Hyper)	20.9	0	17.1	0.9

Anemia

Over the randomized period in the pivotal study (RESPONSE Trial), anemia was more frequent in the JAKAVI arm (43.6%) compared to the BAT arm (30.6%). The CTCAE Grade 3 and 4 events were reported in 1.8% of the patients in the JAKAVI arm and in 0% of the patients in the BAT arm. Female PV patients may be at higher risk of anemia than male PV patients.

At the most recent cut off, over the randomized period in the RESPONSE (32 weeks) and RESPONSE 2 (28 weeks) studies, anemia was reported in PV patients (40.8%). The frequency of the CTCAE Grade 3 and 4 events was 1.1% in PV patients.

Thrombocytopenia

Over the randomized period in the pivotal study, the rate of patients experiencing thrombocytopenia was higher in the JAKAVI arm (24.5%) compared to the BAT arm (18.9%). The frequency of severe (i.e. of CTCAE Grade 3 and 4) thrombocytopenia was 5.4% in the JAKAVI arm and 3.6% in the BAT arm.

At the most recent cut off, over the randomized period in the RESPONSE (32 weeks) and RESPONSE 2 (28 weeks) studies, the rate of patients experiencing thrombocytopenia was 16.8%. The frequency of severe (i.e. of CTCAE Grade 3 and 4) thrombocytopenia was reported in 3.3% patients.

Neutropenia

Over the randomized period in the pivotal study, in PV patients, neutropenia was observed in 2 patients in the JAKAVI arm (1.8%) of which one patient developed CTCAE Grade 4 neutropenia.

At the most recent cut off, over the randomized period in the RESPONSE (32 weeks) and

RESPONSE 2 (28 weeks) studies in PV, neutropenia was observed in 3 patients (1.6%) of which one patient developed CTCAE Grade 4 neutropenia.

Post-Marketing Adverse Drug Reactions

The following adverse reactions have been derived from spontaneous case reports, literature cases and clinical studies. The criteria for including these adverse reactions are based on the seriousness. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and Infestations:
Tuberculosis (including fatal tuberculosis and fatal miliary tuberculosis), progressive multifocal leukoencephalopathy (PML), pneumonia (including fatal pneumonia), sepsis (including fatal sepsis) and endocarditis (including fatal endocarditis), opportunistic fungal infections (including fatal cases) and viral reactivation.

Bleeding:
Cerebral hemorrhage (including fatal case), gastrointestinal bleeding (including fatal cases).

DRUG INTERACTIONS

Drug-Drug 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 to approximately 50% of the dose rounding up to the nearest dosage strength.

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

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 JAKAVI.

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.

Concomitant moderate CYP2C9 and CYP3A4 inhibitors (including a dual enzyme inhibitor as a single agent, e.g. Fluconazole): Based on *in silico* modeling, an AUC increase of ruxolitinib of

102%, 190% or 330% is predicted when co-administered with 100 mg, 200 mg or 400 mg fluconazole, respectively. A 50% dose reduction should be considered when concomitantly administering medicinal products which are moderate inhibitors of CYP2C9 and CYP3A4. Avoid the concomitant use of JAKAVI with fluconazole doses of greater than 200 mg daily.

Effect of ruxolitinib on other agents

Hematopoietic 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 not known.

Drugs that Decrease Heart Rate and/or Prolong the PR Interval: JAKAVI results in a decrease in heart rate and an increase in the PR interval (see **WARNINGS AND PRECAUTIONS**, Cardiovascular & Monitoring and Laboratory Tests; **ADVERSE REACTIONS,** Electrocardiography sections). The concomitant use of JAKAVI with other drugs that lower heart rate and/or prolong the PR interval, such as antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and HIV protease inhibitors should be avoided to the extent possible.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
There are no physical restrictions for patients who receive JAKAVI.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The following safety issues should be considered when developing a dosage regimen in an individual patient:
- Platelet count,
- Absolute neutrophil count,
- Renal impairment,
- Hepatic impairment,
- Concomitant strong CYP3A4 inhibitors,
- Concomitant moderate CYP3A4 and CYP2C9 inhibitors.
- Doses may be titrated based on safety and efficacy.

Recommended Dose and Dosage Adjustment

The recommended starting dose of JAKAVI is based on platelet count and on the indication to be treated (Table 8). A complete blood count and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

Table 8 JAKAVI Starting Doses for patients with myelofibrosis or with polycythemia vera.

Platelet Count	Starting Dose	
	Myelofibrosis	Polycythemia vera
Greater than 200,000/ mm^3	20 mg orally twice daily	10 mg orally twice daily
100,000 to 200,000/ mm^3	15 mg orally twice daily	10 mg orally twice daily
50,000 to <100,000/mm^{3*}	5 mg orally twice daily	5 mg 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 dose of these patients should be titrated cautiously.

Prior to initiating treatment with JAKAVI, the Absolute Neutrophil Count (ANC) of patients should be >1000/mm^3.

Dose modifications based on safety:

Treatment interruptions: Treatment with JAKAVI should be interrupted for :

- platelet counts less than 50,000/mm^3
- absolute neutrophil counts less than 500/mm^3.
- hemoglobin less than 8g/dl (only for PV patients).

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.

Interrupt treatment for bleeding requiring intervention regardless of current platelet count. Once the bleeding event has resolved, consider resuming treatment at the prior dose if the underlying cause of bleeding has been controlled. If the bleeding event has resolved but the underlying cause persists, consider resuming treatment with JAKAVI at a lower dose.

Dose reductions: Dose reductions should be considered if the platelet counts decrease as outlined in Table 9 below, with the goal of avoiding dose interruptions for thrombocytopenia.

Table 9 Dosing Recommendations for Thrombocytopenia

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

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

Dose modifications based on efficacy:

If efficacy is considered insufficient, doses may be increased by a maximum of 5 mg twice daily. The maximum dose of JAKAVI is 25 mg twice daily. The dose should not be increased if the blood counts are not adequate. The platelet counts should be greater than 125,000/mm^3 at the time of dose increase and should never have been below 100,000 mm^3. The ANC levels should be greater than 750/mm^3.

The starting dose should not be increased within the first four weeks of treatment for patients with myelofibrosis and eight weeks of treatment for patients with polycythemia vera and thereafter no more frequently than at 2-week intervals.

Treatment may be continued as long as the benefit: risk balance remains positive. However, the treatment of patients with myelofibrosis should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy. In patients with polycythemia vera, the treatment should be discontinued after 16 months if there has been no clinical benefit since initiation of therapy.

Dose adjustment with concomitant use of strong CYP3A4 inhibitors or moderate CYP2C9 and CYP3A4 inhibitors (e.g. fluconazole):

When JAKAVI is administered with strong CYP3A4 inhibitors or concomitant administration of moderate inhibitors of CYP2C9 and CYP3A4 (including a dual enzyme inhibitor as a single agent, e.g. fluconazole), the dose of JAKAVI should be reduced to approximately 50% of the dose, rounding up to the nearest dosage strength. Avoid the concomitant use of JAKAVI with fluconazole doses of greater than 200 mg daily (see **DRUG INTERACTIONS** section).

More frequent monitoring (e.g. twice a week) of hematology parameters and of clinical signs and symptoms of JAKAVI related adverse reactions is recommended upon initiation of a strong

CYP3A4 inhibitor or moderate CYP2C9 and CYP3A4 inhibitors. If the platelet count decreases to less than 100,000/mm^3, the concomitant use should be avoided when on JAKAVI treatment.

Dosing in special populations

Renal impairment

For patients with moderate (creatinine clearance, CrCl: 30-50mL/min) or severe (CrCl:<30mL/min) renal impairment, the starting dose should be approximately 50% of the recommended dose based on platelet count (table 7). The dose should be rounded up to the nearest dosage strength if necessary.

JAKAVI should be avoided in patients with moderate or severe renal impairment with platelet counts less than 100,000/mm^3.
Patients diagnosed with moderate or severe renal impairment while receiving JAKAVI should be carefully monitored and may need to have their doses titrated to avoid adverse drug reactions.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on hemodialysis. Available data in this population suggest that the starting dose for myelofibrosis patients with ESRD on hemodialysis is 15 mg once a day for patients with platelet count between 100,000-200,000/mm^3 or 20 mg once a day for patients with platelet count of >200,000/mm^3. The recommended starting dose for polycythemia vera patients with ESRD on hemodialysis is 10 mg once a day. JAKAVI is to be administered after hemodialysis has been completed and only on the day of hemodialysis. JAKAVI should not be given more frequently than once a day. Dose modification should be made with careful monitoring of safety and efficacy of individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venous hemofiltration (see **ACTION AND CLINICAL PHARMACOLOGY** section).

Hepatic Impairment

In patients with mild, moderate or severe hepatic impairment, the starting dose should be approximately 50% of the recommended starting dose based on platelet count (table 7). The dose should be rounded up to the nearest dosage strength if necessary.

JAKAVI should be avoided in patients with hepatic impairment with platelet counts less than 100,000/mm^3.

Patients diagnosed with hepatic impairment while receiving JAKAVI should be carefully monitored and may need to have their dose titrated to avoid adverse drug reactions.

Geriatrics (> 65 years of age):

No additional dose adjustments are recommended for elderly patients.

Missed Dose

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

Administration

JAKAVI is dosed orally and can be administered with or without food. Patients should be instructed to swallow the tablet whole. The tablets should NOT be cut, broken, dissolved, crushed or chewed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ruxolitinib is a selective inhibitor of the Janus Kinases (JAKs) JAK1 (IC_{50} 3.3 nM) and JAK2 (IC_{50} 2.8 nM). 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 $JAK2^{V617F}$, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signaling regardless of $JAK2^{V617F}$ mutation status. Activating mutations in JAK2 (such as $JAK2^{V617F}$ or other exon 12 mutations) 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 $JAK2^{V617F}$ mutated protein, with IC_{50}'s ranging from 80-320 nM. In a mouse model of $JAK2^{V617F}$-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased $JAK2^{V617F}$ 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

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects as well as 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.

In a double-blind, placebo-controlled, crossover ECG study in healthy subjects (N=49), there was no indication of a QTc prolonging effect of ruxolitinib at single doses of 25 mg and 200 mg.

Pharmacokinetics

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. Dose proportionality was demonstrated in the single and multiple dose studies. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5-200 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.

Metabolism: *In vitro* studies indicate that CYP3A4 is 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* and *in vivo* studies.

Excretion: 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.

Special Populations and Conditions

Pediatrics: The safety and effectiveness of JAKAVI in pediatric patients have not been established.

Geriatrics: No additional dose adjustments are recommended for elderly patients. Based on population pharmacokinetic evaluations, no relationship was apparent between oral clearance and age of patients.

Gender or race: Based on population pharmacokinetic evaluations, no relationship was apparent between oral ruxolitinib clearance and patient race.

In myelofibrosis patients, clearance was lower in women (17.7 L/h) compared to men (22.1 L/h), with 39% inter-subject variability. In polycythemia vera patients, clearance was 12.7 L/h, with a 42% inter-subject variability, and no relationship was apparent between oral clearance and gender in this patient population. The reason for the lower ruxolitinib clearance in polycythemia vera patients compared to myelofibrosis patients is unknown.

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 [Child-Pugh A (n=8)], moderate [Child-Pugh B (n=8)] and severe hepatic impairment [Child-Pugh C (n=8)] 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 **DOSAGE AND ADMINISTRATION** section).

Renal Insufficiency: Following a single ruxolitinib dose of 25 mg, the C_{max} and AUC of the parent compound was similar in subjects with mild [CrCl 44-74 mL/min (n=8)], moderate [CrCl 35-47 mL/min (n=8)], or severe [CrCl 7-28 mL/min (n=8)] renal impairment and in those with normal renal function (CrCl 79-122 mL/min in 8 healthy subjects). However, relative 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 (HD). The relative AUC values of the metabolites corresponded to 61% of the parent compound AUC in healthy normal subjects and increased to 79%, 117% and 173% in subjects with mild, moderate or severe renal impairment, respectively. It increased further to 346% in subjects with ESRD who received HD before dose and to 297% in subjects with ESRD who received HD after dose. The overall pharmacological activity (ruxolitinib + metabolites) was 117% for subjects with normal renal function, 123%, 134%, 153%, 212%, and 192% in subjects with mild, moderate, severe renal impairment, ESRD who received HD before dose, and ESRD who received HD after dose, respectively. Based on the overall pharmacological activity (ruxolitinib + metabolites) and potential metabolite accumulation in renal patients, dose modifications is conservatively proposed in the moderate, severe renal impaired and ESRD patients (see **DOSAGE AND ADMINISTRATION** section).

STORAGE AND STABILITY

Store between 15 - 25°C.

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

SPECIAL HANDLING INSTRUCTIONS

No special handling requirements.

Special precautions for disposal

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

JAKAVI (*ruxolitinib* tablets) is available in four strengths. Each tablets contains 5 mg, 10 mg, 15 mg or 20 mg ruxolitinib free base (as ruxolitinib phosphate).

JAKAVI (ruxolitinib tablets*) 5 mg tablets:*
Round curved white to almost white tablets with "NVR" debossed on one side and "L5" debossed on the other side.

JAKAVI (ruxolitinib tablets*) 10 mg tablets:*
Round curved white to almost white tablets with "NVR" debossed on one side and "L10" debossed on the other side.

JAKAVI (ruxolitinib tablets*) 15 mg tablets:*
Ovaloid curved white to almost white tablet with "NVR" debossed on one side and "L15" debossed on the other side.

JAKAVI (ruxolitinib tablets*) 20 mg tablets:*
Elongated curved white to almost white tablet with "NVR" debossed on one side and "L20" debossed on the other side.

Non-medicinal ingredients: hydroxypropylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate (Type A), 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.

Availability
JAKAVI (ruxolitinib tablets) 5 mg, 10 mg, 15 mg and 20 mg tablets are supplied in blister packaging (4x14 tablets).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ruxolitinib phosphate

Chemical name: (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate

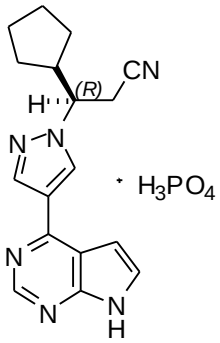
1*H*-Pyrazole-1-propanenitrile,β-cyclopentyl-4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-,(β*R*)-, phosphate (1:1)

Molecular formula: Salt form on anhydrous basis: $C_{17}H_{18}N_6.H_3PO_4$

Molecular mass: Salt form on anhydrous basis: 404.36
Free base form: 306.37

Salt/base ratio on anhydrous basis: 1.320

Structural formula:



Physicochemical properties:

Physical Description: White to almost white powder

Solubility: Ruxolitinib phosphate is highly soluble in water. Ruxolitinib phosphate solubility in aqueous medium is pH dependent. Ruxolitinib phosphate is soluble in apolar organic solvents at 25°C and 50°C.

pH:	The pH value of a saturated solution of ruxolitinib phosphate in water (46 mg/mL) was measured potentiometrically at room temperature and was determined to be 2.5.
pKa:	4.3 and 11.8
Partition Coefficient:	Ruxolitinib phosphate in octanol/aqueous buffers exhibits a partition coefficient of less than 1 in the octanol/pH 1.0 buffer system and becomes more hydrophobic at pH 7.4 (the physiological pH of blood serum).
Melting point:	194 - 198°C (as determined by differential scanning calorimetry (DSC)).

CLINICAL TRIALS

Myelofibrosis

Study demographics and trial design

The clinical efficacy of JAKAVI in patients with Myelofibrosis (Primary Myelofibrosis (MF), Post-Polycythemia Vera Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-MF)), has been demonstrated based on the two Phase III Studies (COMFORT I and COMFORT II).

Table 10 Summary of patient demographics for MF clinical trials (Intent To Treat (ITT)

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
COMFORT-I	Phase 3 double-blind, randomized, placebo-controlled study of the JAK inhibitor ruxolitinib in adult patients with MF, including PMF, PPV-MF, or PET-MF.	Ruxolitinib and the placebo were administered orally: Starting dose based on baseline platelet count: -between 100,000 and 200,000/mm^3 15 mg b.i.d. - > 200,000/mm^3 20 mg b.i.d.	Total number of patients: 309 Ruxolitinib: 155 Placebo: 154	Ruxolitinib: 45.2% ≤ 65 years 54.8% > 65 years Mean: 66.7 Range: 43.0, 91.0 Placebo: 33.8% ≤ 65 years 66.2% > 65 years Mean: 68.7 Range: 40.0, 86.0	Ruxolitinib: M: 51% F: 49% Placebo: M: 57.1% F: 42.2%
COMFORT-II	Phase 3 open-label, randomized study of the JAK inhibitor ruxolitinib versus best available therapy (BAT) in adult patients with MF, including PMF, PPV-MF, or PET-MF.	Ruxolitinib and BAT were administered orally: Starting dose based on baseline platelet count: between 100,000 and 200,000/mm^3 15 mg b.i.d. - > 200,000/mm^3 20 mg b.i.d.	Total number of patients: 219 Ruxolitinib: 146 BAT: 73	Ruxolitinib: 47.3% ≤ 65 years 52.7% > 65 years Mean: 65.1 Range: 35.0, 83.0 BAT: 49.3% ≤ 65 years 50.7% > 65 years Mean: 65.2 Range: 35.0, 85.0	Ruxolitinib: M: 56.8% F: 43.2% BAT: M: 57.5% F: 42.5%

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 Prognostic Scoring System (IPSS). The prognostic factors that comprise the IPSS 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.

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 the proportion of subjects achieving ≥ 35% reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computerized Axial Tomography (CAT).

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 the 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 based on investigator assessment. 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 based on investigator assessment. 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.

Study results

Efficacy analyses of the primary endpoint in COMFORT-I and COMFORT-II are presented in Table 1 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 11 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 analysis)

	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. In an exploratory analysis, 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 $JAK2^{V617F}$ 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

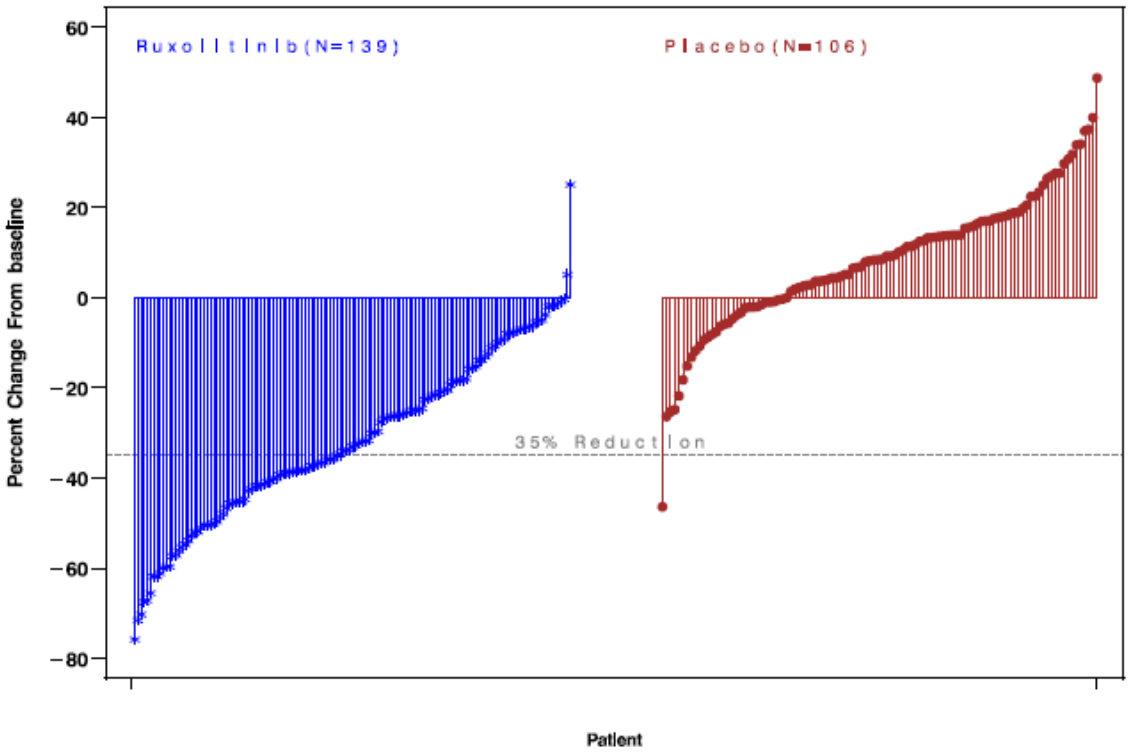
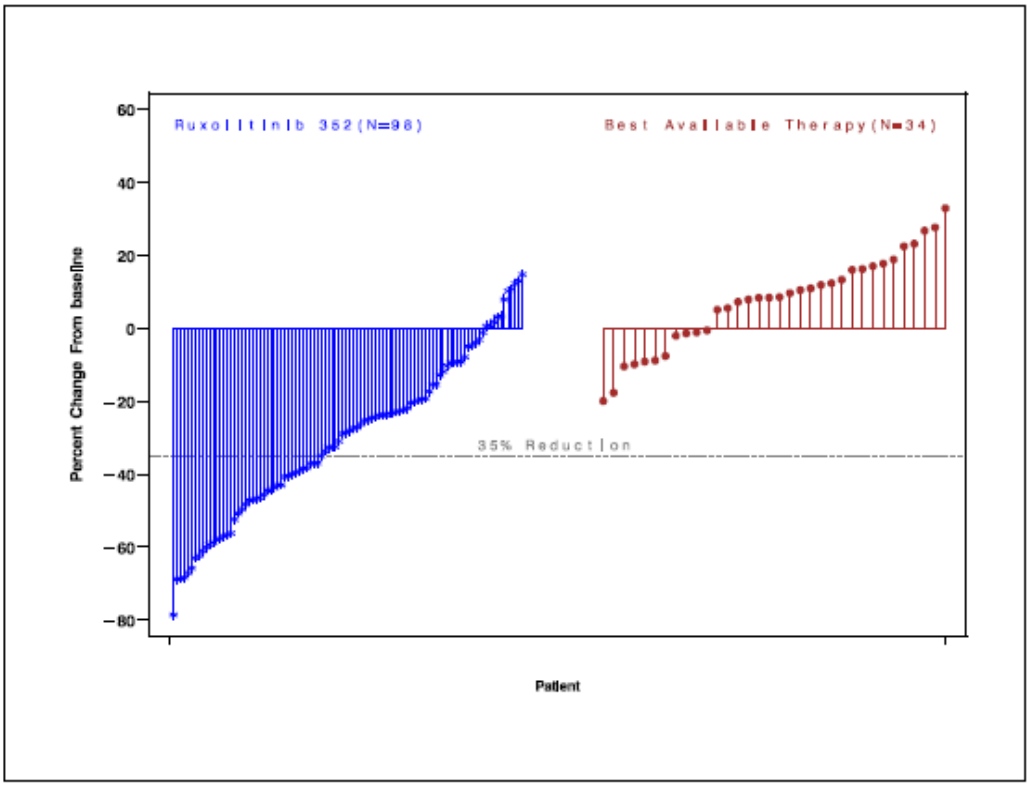


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at week 48 in COMFORT-II. Among the 98 patients in the JAKAVI group who had both baseline and week 48 spleen volume evaluations, the median reduction in spleen volume at week 48 was 28%. Among the 34 patients in the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



JAKAVI improves myelofibrosis-associated symptoms 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 modified MFSAF is a daily diary capturing the core symptoms of myelofibrosis (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety). Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60. A significantly larger proportion of subjects in the JAKAVI group achieved a $\geq$ 50% improvement from Baseline in the week 24 total symptom score compared with the placebo group (45.9% and 5.3%, respectively, $p < 0.0001$ using the Chi-Squared test).

In an exploratory analysis, an improvement in overall quality of life was measured by a validated instrument, the EORTC QLQ-C30 in both COMFORT-I and COMFORT-II. At week 24 in COMFORT-I the mean change for the global health status/quality of life score was +12.3 and -3.4 (p<0.0001) for JAKAVI and placebo, respectively.

In COMFORT-I, at the updated final analysis, conducted after a median follow–up of 5.2 years, a total of 69 (44.5%) and 82 (53.2%) patients died in the ruxolitinib and placebo arms, respectively (HR 0.69; 95% CI: 0.50-0.96, p=0.025).

In COMFORT-II, at the updated final analysis, conducted after a median follow–up of 4.7 years, a total of 94 patients died overall, 59 (40.4%) and 35 (47.9%) patients died in the ruxolitinib and Best available therapy (BAT) arms, respectively (HR 0.67; 95% CI: 0.44-1.02, *p*=0.062).

Polycythemia vera

Study demographics and trial design

The clinical efficacy of JAKAVI in patients with Polycythemia vera has been demonstrated based on a Phase III study (RESPONSE).

Table 12 Summary of patient demographics for the PV clinical trial (ITT)

Study	Trial design	Dosage and route of administration	Study subjects (n=number)	Mean age (Range)	Gender
RESPONSE (Study B2301)	Phase 3, open-label, randomized, controlled study comparing the efficacy and safety of the JAK inhibitor ruxolitinib to Best Available Therapy (BAT) in adult patients with PV who were resistant to or intolerant of hydroxyurea. The patients randomized to the BAT could crossover to ruxolitinib at week 32 if they failed to meet the primary endpoint, and after week 32 if they did not achieve HCT control (absence of phlebotomy eligibility) or had a spleen volume progression.	Ruxolitinib was administered orally at a starting dose of 10 mg twice daily (doses were then adjusted in individual patients based on tolerability and efficacy) BAT was selected on a patient-by-patient basis and included hydroxyurea (59.5% of patients), interferon/pegylated interferon (11.7% of patients), anagrelide (7.2% of patients), pipobroman (1.8% of patients) and observation (15.3% of patients)	Total number of patients: 222 Ruxolitinib: 110 BAT: 112	Ruxolitinib: Median age: 62 years Mean: 61.1 years (34-90 years) BAT: Median age: 60 years Mean: 59.1 years (33-84 years)	Ruxolitinib: M: 60% F: 40% BAT: M: 71.4% F: 28.6%

The study was conducted in 222 patients with polycythemia vera who were resistant to or

intolerant of hydroxyurea as per the modified European Leukemia Net (ELN) international working group consensus.

Baseline demographics and disease characteristics were comparable between the two treatments groups. The median age was 60 years (range 33 to 90 years). The proportion of patients with the $JAK2^{V617}$ mutation was 94.5% (104) in the JAKAVI group and 95.5% (107) in the BAT group respectively. For patients in the JAKAVI group and the BAT group, the median time since the diagnosis of PV was 8.2 years and 9.3 years respectively and they had previously received hydroxyurea for a median duration of approximately 3 years in both groups. Most patients (> 80%) had received at least two phlebotomies in the last 24 weeks prior to screening. All patients had splenomegaly ($\geq$450 mm^3) at study entry and their hematocrit was to be normalized to levels between 40-45% within 14 days before the day 1 visit. All randomized subjects in the study received concomitant low dose aspirin (75-150 mg/day) unless medically contraindicated. In this case, other prophylactic antithrombotic agents may have been used.

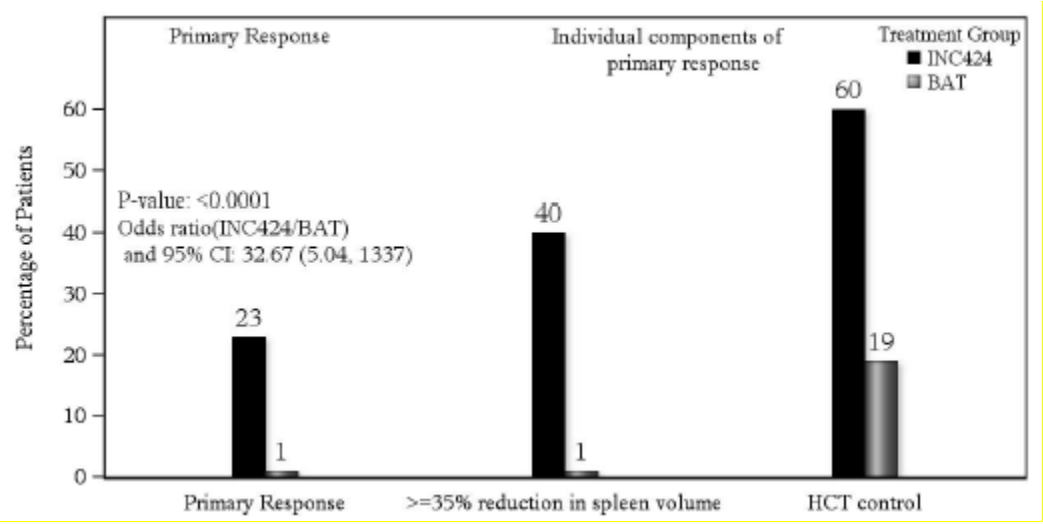
Study Results:

The primary endpoint was the proportion of patients achieving both the absence of phlebotomy eligibility (hematocrit (HCT) control) and $\geq$ 35% reduction in spleen volume from baseline at week 32. Hematocrit control was defined as the absence of phlebotomy eligibility beginning at the week 8 and continuing through week 32, with no more than one phlebotomy eligibility occurring post-randomization and prior to week 8. 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 with complete hematological remission defined as achieving hematocrit control, platelet count less than or equal to 400 X 10^9/L, and white blood cell count less than or equal to 10 X 10^9 /L.

A higher proportion of patients in the JAKAVI group achieved the primary composite endpoint and each of its individual components. Significantly more patients in the JAKAVI group (23%) compared to the BAT group (0.9%) achieved the primary composite endpoint ($p<0.0001$). Hematocrit control was achieved in 60% of patients in the JAKAVI group compared to 18.75% in the BAT group and $\geq$ 35% reduction in spleen volume was achieved in 40% of patients in the JAKAVI group compared to 0.9% in the BAT group (Figure 3).

Both key secondary endpoints were also met: The proportion of patients achieving a complete hematologic remission at week 32 was 23.6% in the JAKAVI group compared to 8.0% in the BAT group ($p=0.0013$), and the proportion of patients achieving a durable primary response at week 48 was 20% in the JAKAVI group and 0.9% in the BAT group ($p<0.0001$), which represent 91.3% (n=21/n=23) of patients in the JAKAVI group who achieved the primary endpoint at week 32 and maintained it at week 48.

Figure 3 Patients achieving the primary endpoint and components of the primary endpoint at Week 32



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% (n=91) of patients were still on treatment at the time of the Week 80 data cut-off. Of patients (n=25) who achieved a primary response at Week 32, 80% (n=20) maintained their response for at least 48 weeks after the initial response.

RESPONSE 2 is a randomized, open label, active-controlled phase IIIb study. The primary endpoint was defined as the proportion of patients achieving HCT control (absence of phlebotomy eligibility) at Week 28. The study met its primary objective with a higher proportion of patients who were resistant to or intolerant of hydroxyurea but without palpable splenomegaly in the JAKAVI arm (62.2%, n=46) compared to the BAT arm (18.7%, n=14) achieving the primary endpoint of HCT control ($p<0.0001$).

DETAILED PHARMACOLOGY

Pharmacodynamics

In vitro data demonstrate that ruxolitinib is an inhibitor of JAK1 (IC_{50} 3.3 ± 1.2 nM) and JAK2 (IC_{50} 2.8 ± 1.2 nM), compared to the other two JAK family members, TYK2 (IC_{50} 19 ± 3.2 nM) and JAK3 (IC_{50} 428 ± 243 nM). Moreover ruxolitinib inhibits proliferation (IC_{50} 141 nM) and STAT3 phosphorylation (IC_{50} 125 nM) in a cytokine dependent, JAK wild-type INA-6 multiple myeloma cell line. Additionally, inhibition of proliferation (IC_{50} 127 nM) and JAK2/STAT5/ERK phosphorylation (IC_{50} 128-320nM) was observed in a pro-B-cell Ba/F3 cell line rendered cytokine-independent and $JAK2^{V617F}$-dependent by expression of $JAK2^{V617F}$ and the erythropoietin receptor (EpoR).

In vivo, ruxolitinib was examined in models relevant to myeloproliferative neoplasms (MPN). Treatment of mice with ruxolitinib resulted in a dose-dependent suppression of phosphorylated STAT3 and tumor growth in the cytokine-dependent, JAK wild type INA-6 multiple myeloma xenograft model. In the mutant $JAK2^{V617F}$ -driven Ba/F3-EpoR xenograft mouse model ruxolitinib treatment suppressed splenomegaly mutant allele burden (33% decrease, $P < 0.01$), and circulating inflammatory cytokines (TNF-α and IL-6). Furthermore, treatment of mice with ruxolitinib normalized aberrantly activated JAK/STAT signaling, as indicated by assessing levels of phosphorylated STAT3 in spleen lysates. Mice bearing Ba/F3-EpoR-$JAK2^{V617F}$ cells and treated with ruxolitinib had a significantly improved survival compared to animals treated with vehicle. After 3 weeks of treatment, > 90% of vehicle-treated mice had succumbed to disease while > 90% of ruxolitinib-treated mice survived.

Safety pharmacology

Ruxolitinib was evaluated in a safety pharmacology core battery of studies that included CNS and respiratory studies in the rat, a cardiovascular study in telemeterized conscious dogs, and in an *in vitro* hERG channel assay.

Safety pharmacology of ruxolitinib in vitro did not demonstrate strong inhibition of hERG (IC_{50} 132μM) in a transfected cell line originally derived from human embryonic kidney cells (HEK293). In vivo safety pharmacology of ruxolitinib in rats and dogs yielded adverse effects in respiratory, CNS and cardiovascular function at exposures that exceeded those observed in human studies. The effects in the respiratory study included lower respiratory rates, higher tidal volumes and lower minute volumes and occurred at an exposure approximately 50-fold or 22 fold the exposure at the maximum human recommended dose (based on free C_{max} or AUC, respectively). The effects in the CNS studies were characterized by lower body temperature, lower activity and they occurred at an exposure approximately 2.6-fold or 0.7-fold (in males based on free C_{max} or AUC, respectively) and 50-fold or 22-fold (in females based on free C_{max} or AUC, respectively) the exposure at the maximum human recommended dose. In the cardiovascular assessment study, lower systolic and diastolic pressure, increased heart rate, decreased mean and pulse arterial pressure were observed at an exposure approximately 36-fold or 49-fold the exposure at the maximum human recommended dose (based on free C_{max} or AUC,

respectively). These in vivo safety pharmacology observations have not been observed in the repeat-dose toxicity studies or recapitulated in the clinical studies.

Pharmacokinetics

ADME studies were performed in mouse, rat, minipig and dog. Notably, these studies revealed that ruxolitinib was neither an inhibitor nor a substrate of P-gp. Ruxolitinib is highly soluble (pH 1.0-8.0) and permeable with a range of bioavailability (22-105%) dependant on the species. In humans, greater than 45% of ruxolitinib was absorbed after oral administration, which was similar to that of dogs. The mean ex vivo unbound plasma fraction post ruxolitinib treatment was 2.7-4.9% in mice, 18% in rats, 13% in rabbits, 9.7% in dogs and 33% in minipigs. Similar values were observed for their in vitro unbound fractions. The mean in vitro unbound fraction for human plasma was 3.3%. Upon entry into circulation, ruxolitinib was rapidly and widely distributed in rats (i.e. to gastrointestinal system, urinary bladder, liver, renal cortex, aorta and adrenal glands, skin, kidney) with maximal serum levels detected 0.5-2 hours post-oral administration. Notably, ruxolitinib and its metabolites crossed the blood brain barrier (<10% of plasma concentrations) and placental barrier of rats. Ruxolitinib and its metabolites transferred substantially into the milk of lactating rats. Ruxolitinib related radioactivity was eliminated within 24 hours. In bile duct cannulated rats, a majority of radioactivity was recovered in the urine (50%) followed by bile (37%) and feces (12%). In dogs, radioactivity was recovered in the urine (34-36%) and feces (55-58%). Renal excretion of unchanged ruxolitinib was very limited (<1% of dose).

In vivo metabolism of ruxolitinib resulted in over 50 metabolites across various animal species. In humans, most of these metabolites had some PD activity as measured by activated STAT3. Ruxolitinib was eliminated predominantly by oxidative metabolism followed in some cases by limited subsequent glucuronidation in humans and animal species. The main circulating human metabolite was identified as M18, which represented 25% of parent compound exposure. Like ruxolitinib, M18 did not inhibit efflux (MXR and MDR1) and uptake transporters (OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2). Moreover, M18 did not inhibit CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6.

Human studies on drug interactions
Clinically relevant drug interactions are discussed in Part I (see **DRUG INTERACTIONS** section).

CYP3A4 inducers:
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 exposure of the active metabolites to parent compound doubled as a result of rifampin co-administration. The overall pharmacodynamic marker pSTAT3 inhibition was reduced by only 10% which may be explained by the increased exposure of the active metabolites as well as decreased exposure of the parent compound.

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 contraceptive efficacy of this combination is not expected to be compromised by co-administration with ruxolitinib.

TOXICOLOGY

Single oral dose toxicity

Ruxolitinib was well tolerated following single oral doses of up to 100 mg/kg in rats and 40 mg/kg in dogs. Mild lethargy and emesis were respectively observed at a dose of 100mg/kg in rats (exposure approximately equal or 6.4-fold the exposure at the maximum human recommended dose based on AUC in males and females, respectively) or 40 mg/kg in dogs (exposure approximately 7.9-fold the exposure at the maximum human recommended dose based on AUC). In the rat study assessing the CNS function, darkened mucous membranes and skin were noted at an exposure approximately 0.10-fold or 3.8-fold the exposure at the maximum human recommended dose (based on AUC, in males and females, respectively).

Repeated oral dose toxicity

Repeated oral dose studies with ruxolitinib of up to 4 weeks in mice, 6 months in rats, and 12 months in the dog were conducted.

Target organs associated with the pharmacological action of ruxolitinib in repeat dose studies include bone marrow, peripheral blood and lymphoid tissues at an exposure approximately 3-fold or 0.7-fold the exposure at the maximum human recommended dose based on AUC in rats and dogs, respectively. Findings were reversible or demonstrated a tendency for reversibility. Specific findings include, decreases in lymphocytes, eosinophils, reticulocytes, red blood cell, hemoglobin and hematocrit as well as hypocellularity of the bone marrow and lymphoid organs (spleen, thymus, lymph nodes). Dogs (6 & 12 month study) developed bacterial, parasitic and viral infections that are generally associated with immunosuppression (at an exposure approximately equal to the exposure at the maximum human recommended dose based on AUC).

Other findings include gastrointestinal inflammation (4 week dog study; at an exposure approximately 5-fold the exposure at the maximum human recommended dose based on AUC), prostatic atrophy (6 month dog study; at an exposure approximately 1.9-fold the exposure at the maximum human recommended dose based on AUC), heart fibrosis (13 week female rat study; at an exposure approximately 9.5-fold the exposure at the maximum human recommended dose based on AUC), adrenal cortical atrophy (6 month rat study; at an exposure approximately 0.14-fold the exposure at the maximum human recommended dose based on AUC), hyperplasia of non-glandular stomach (4 week mouse study; at an exposure approximately 6.5-fold the exposure at the maximum human recommended dose based on AUC), increases of ALP and GGT (13 week female rat study; at an exposure approximately 9.6-fold the exposure at the maximum human recommended dose based on AUC), and decreases in phosphorous and

calcium levels (dog ≥5mg/kg/day; at an exposure approximately 1.6-fold the exposure at the maximum human recommended dose based on AUC).

Genotoxicity

As a single agent, ruxolitinib did not test positive for mutagenicity in a bacterial mutagenicity assay (Ames test) or clastogenicity in an *in vitro* chromosomal aberration assay (cultured human peripheral blood lymphocytes) or *in vivo* rat bone marrow micronucleus assay.

Carcinogenesis

In a 6-month carcinogenicity study, no significant increase in neoplastic lesions was observed in the Tg.RasH2 transgenic mouse model at C_{max} and AUC exposures that exceeded (8-fold) those observed in clinical studies. Non-neoplastic intranasal inflammation was observed in the treated mouse model at an exposure approximately 8-fold the exposure at the maximum human recommended dose based on AUC. Together, ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model nor in a 2-year study in rats.

Reproductive and developmental toxicity studies

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 BID, 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 was not teratogenic but was associated with maternal toxicity, embryolethality (increases in post implantation loss resulting in decreased litter sizes) and fetotoxicity (decreased fetus weights) in rats and rabbits. No effects were noted on reproductive performance or fertility. In a pre- and post-natal development study, there were no adverse findings for fertility indices and maternal and embryofetal survival, growth, and developmental parameters. All of the observations in this section occur at exposures that are significantly less than those observed in the clinical populations (at an exposure approximately 0.07 to 0.34-fold the maximum human recommended dose based on AUC).

Phototoxicity

Ruxolitinib absorbs light in the range of 290 to 700 nm, with a peak at 310 nm. In studies performed on guinea pigs, ruxolitinib did not show any photoallergic or phototoxic potential when applied either topically or dermally at concentrations ≤ 1.5%. Repeated daily topical administration with or without simulated sunlight in hairless mice for a period of 13 weeks did not result in adverse findings. No phototoxicity or photoallergy or irritancy studies have been performed via the oral route of administration.

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PART III: CONSUMER INFORMATION

PrJAKAVI®

(ruxolitinib tablets)
(as ruxolitinib phosphate)

This leaflet is part III of a three-part "Product Monograph" published when JAKAVI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about JAKAVI. Contact your healthcare professional (doctor, pharmacist or nurse) if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

JAKAVI is a prescription drug used to treat adult patients with enlarged spleen and/or its associated symptoms caused by myelofibrosis, a rare form of blood cancer.

JAKAVI is also used to control the haematocrit (the amount of red blood cells in the blood) in adult patients with polycythemia vera who are unable to use or who do not have their hematocrit controlled with a cytoreductive agent.

JAKAVI should be prescribed and monitored by a physician experienced in the use of anti-cancer therapies.

What it does:

Myelofibrosis is a disorder of the bone marrow, in which the marrow is replaced by scar tissue. JAKAVI is a kinase inhibitor that works at reducing spleen size and/or its associated symptoms caused by myelofibrosis.

Polycythemia vera is a disorder of the bone marrow, in which the marrow produces too many red blood cells. This makes the blood thicker. JAKAVI is a kinase inhibitor that can reduce the amount of red blood cells in the blood in patients with polycythemia vera.

When it should not be used:

Do not take JAKAVI if you:

- **are allergic** (hypersensitive) to ruxolitinib, or any of the other ingredients of JAKAVI listed under "*What the nonmedicinal ingredients are*".
- have or have had a disease called progressive multifocal leukoencephalopathy (PML).

What the medicinal ingredient is:

Ruxolitinib phosphate.

What the nonmedicinal ingredients are:

microcrystalline cellulose, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate (Type A), povidone.

What dosage forms it comes in:

Tablets; 5 mg, 10 mg, 15 mg and 20 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious infections have been reported in patients treated with JAKAVI. Some cases were life-threatening or lead to death.

BEFORE you use JAKAVI talk to your doctor or pharmacist if you:

- have any type of infections. It may be necessary to treat your infection before starting JAKAVI. It is important that you tell your doctor if you have ever had tuberculosis or if you have been in close contact with someone who has had or has tuberculosis. Your doctor may test you to see if you have tuberculosis.
- have any kidney problems.
- have or have ever had liver problems.
- have any heart problems, including low heart rate, or if you ever have fainting spells.
- have intolerance to lactose (milk sugar). JAKAVI contains lactose.
- are pregnant or plan to become pregnant. JAKAVI is not recommended during pregnancy. You must use an effective method of birth control to avoid becoming pregnant while taking JAKAVI.
- are breast –feeding. JAKAVI may harm your baby.
- are a male patient. You must take appropriate precautions to avoid fathering a child during JAKAVI treatment.
- have ever had skin cancer.
- have ever had viral hepatitis B (a liver disease).

Children and adolescents (under 18 years old)

The safety of JAKAVI in patients younger than 18 years old have not been established.

During your treatment with JAKAVI

Tell your doctor straight away:

- If you experience unexpected bruising and/or bleeding, unusual tiredness, shortness of breath with exercise or at rest, looking pale, or frequent infections (signs of blood disorders).

- If you experience fever, chills or any symptoms of infections or if you develop painful skin rash with blisters (signs of shingles).
- If you experience chronic cough with blood-tinged sputum, fever, night sweats, and weight loss (these are signs of tuberculosis).
- If you have any of the following symptoms or if anyone close to you notices that you have any of these symptoms: confusion or difficulty thinking, loss of balance or difficulty walking, clumsiness, difficulty speaking, decreased strength or weakness on one side of your body, blurred and/or loss of vision (these are signs of progressive multifocal leukoencephalopathy).
- If you notice any skin changes. This may require further observation, as certain types of skin cancer (non-melanoma) have been reported with the use of JAKAVI. You should minimize your exposure to sunlight and other sources of UV light, such as tanning beds, while taking JAKAVI.
- If you have fever, cough, difficult or painful breathing, wheezing, pain in chest when breathing (possible symptoms of pneumonia).

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

It is particularly important that you mention any of the following medicines:

- some medicines used to treat infections. These include medicines which treat fungal diseases (antifungals like fluconazole, ketoconazole, itraconazole, posaconazole and voriconazole, or medicines to treat types of bacterial infections (antibiotics like clarithromycin, or telithromycin), or medicines to treat viral infections, including HIV/AIDS (atazanavir, indinavir, nelfinavir, ritonavir, saquinavir).
- Any medications that you are taking that affect the heart or blood pressure, such as antiarrhythmics, digitalis glycosides, antihypertensives and cimetidine (a medicine to treat heartburn).

While you are taking JAKAVI you should never start a new medicine without checking first with the doctor who has prescribed you JAKAVI. This includes prescribed medicines, over the counter medicines and herbal or alternative medicines.

PROPER USE OF THIS MEDICATION

Follow your doctor's instructions carefully. Do not take more JAKAVI than what your doctor told you.

Usual adult dose:

Patients with Myelofibrosis: 15 mg or 20 mg by mouth twice daily

Patients with Polycythemia vera: 10 mg by mouth twice daily

The maximum dose is 25 mg twice daily.

It is important to take JAKAVI at about the same time every day. If you require hemodialysis, you only need to take a single dose of JAKAVI after each hemodialysis session.

JAKAVI can be taken either with or without food. **Swallow whole** with a glass of water. Do NOT cut, break, dissolve, crush or chew the tablet.

How long to take JAKAVI

You should continue taking JAKAVI for as long as your doctor tells you to. This is a long-term treatment. Your doctor will regularly monitor your condition to make sure that the treatment is having the desired effect.

If you have questions about how long to take JAKAVI, talk to your doctor or pharmacist.

Monitoring during your treatment with JAKAVI

Before you start treatment with JAKAVI, your doctor will perform blood tests to determine the starting dose for you. Your doctor will carefully check if you have any signs or symptoms of infection before starting and during your treatment with JAKAVI.

You will have some blood tests during your treatment with JAKAVI to monitor the amount of blood cells in your body (white and red blood cells, platelets), and your kidney and liver functions. These tests are performed to see how you respond to the treatment, or to see if JAKAVI is having an unwanted effect. Your doctor may need to adjust the dose of JAKAVI or interrupt your treatment with JAKAVI. You will also have other tests during your treatment with JAKAVI to monitor the condition of your heart beat and blood pressure. Your doctor may also regularly check the level of lipids (fat) in your blood.

Overdose:

If you take more JAKAVI than you should or in case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Do not use a double dose of JAKAVI to make up for a forgotten dose. If you forgot to take JAKAVI simply take your next dose at the scheduled time.

If you stop taking JAKAVI

If you are taking JAKAVI to treat myelofibrosis and you interupt your treatment, your myelofibrosis related symptoms may come back. Therefore, you should not stop taking JAKAVI while being treated for myelofibrosis without checking first with your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- High level of cholesterol (hypercholesterolemia) or fat (hypertriglyceridemia) in the blood
- Dizziness
- Headache
- Abnormal liver function test results
- Weight gain
- Frequently passing gas (flatulence), diarrhea, nausea
- Muscle spasms
- Ringing in the ears
- Back pain
- Numbness
- Anxiety
- Cough, pain in the mouth and/or throat
- Nose bleeds
- Constipation
- High blood pressure (hypertension) may also be the cause of dizziness and headache

If any of these affects you severely, tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common			
-Urinary tract infection: Symptoms like frequent urination, painful urination, blood in the urine		√	
-Tiredness, fatigue, shortness of breath, pale skin (symptoms of anemia which is caused by low level of red blood cells)		√	
-Frequent infections, fever, chills, sore throat or mouth ulcers due to infections (symptoms of neutropenia which is caused by low level of white blood cells)		√	
-Spontaneous bleeding or bruising (symptoms of thrombocytopenia which is caused by low levels of platelets)		√	
Common			
- Painful skin rash with blisters (symptoms of shingles)		√	
-Any sign of bleeding in the brain, such as sudden altered level of consciousness, persistent headache, numbness, tingling, weakness or paralysis			√
-Any sign of bleeding in the stomach or intestine, such as passing black or bloodstained stools, or vomiting blood.			√
- Any sign of heart problems such as low heart beat, chest pain, dizziness, vertigo, fainting			√
- Palpitation		√	
Uncommon			
-Chronic cough with blood-tinged sputum, fever, night sweats, and weight loss (symptoms of tuberculosis)			√
Unknown frequency			

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Confusion or difficulty thinking, loss of balance or difficulty walking, clumsiness, difficulty speaking, decreased strength or weakness on one side of your body, blurred and/or loss of vision (symptoms of progressive multifocal leukoencephalopathy).			√

This is not a complete list of side effects. For any unexpected effects while taking JAKAVI contact your doctor or pharmacist.

HOW TO STORE IT

- Do not take JAKAVI after the expiry date shown on the box.
- Store between 15-25 ºC.
- Store in the original package.
- Keep out of the reach and sight of children.

Disposal of unused medicines should follow local rules and requirements.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;(www.healthcanada.gc.ca/medeffect)
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.novartis.ca

or by contacting the sponsor
Novartis Pharmaceuticals Canada Inc., at:
1-800-363-8883

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