NOVARTIS

JAKAVI® (ruxolitinib)

5, 15 and 20 mg tablets

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1. SCHEDULING STATUS: S4

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

JAKAVI® 5 mg tablets

Each tablet contains 5 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 71.45 mg lactose monohydrate.

JAKAVI® 10 mg tablets

Each tablet contains 10 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 142.90 mg lactose monohydrate.

JAKAVI® 15 mg tablets

Each tablet contains 15 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 214.35 mg lactose monohydrate.

JAKAVI® 20 mg tablets

Each tablet contains 20 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 285.80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

JAKAVI 5 mg tablets

Round curved, white to almost white tablets of approximately 7.5 mm in diameter with “NVR” debossed on one side and “L5” debossed on the other side.

JAKAVI 10 mg tablets

Round curved, white to almost white tablets of approximately 9.3 mm in diameter with “NVR” debossed on one side and “L10” debossed on the other side.

JAKAVI 15 mg tablets

Ovaloid curved, white to almost white tablets of approximately 15.0 x 7.0 mm with “NVR” debossed on one side and “L15” debossed on the other side.

JAKAVI 20 mg tablets

Elongated curved, white to almost white tablets of approximately 16.5 x 7.4 mm with “NVR” debossed on one side and “L20” debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Myelofibrosis (MF)

JAKAVI is indicated for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

Polycythaemia vera (PV)

JAKAVI is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

Graft-versus-host disease (GvHD)

JAKAVI is indicated for the treatment of patients with steroid refractory graft-versus-host disease aged 6 years and older who have inadequate response to corticosteroids or other systemic therapies.

4.2 Posology and method of administration

JAKAVI treatment should only be initiated by a medical practitioner experienced in the administration of anti-cancer medicines.

A complete blood cell count, including a differential white blood cell count, must be performed before initiating therapy with JAKAVI.

Complete blood count, including a differential white blood cell count, should be monitored every 2 - 4 weeks until JAKAVI doses are stabilised, and then as clinically indicated (see section 4.4).

Posology

Starting dose

The recommended starting dose of JAKAVI in myelofibrosis (MF) is based on platelet counts (see Table 4-1).

Table 4-1 Starting doses in myelofibrosis

Platelet count	Starting dose
Greater than 200,000/mm^3	20 mg orally twice daily
100,000 to 200,000/mm^3	15 mg orally twice daily
50,000 to less than 100,000/mm^3	10 mg orally twice daily

The recommended starting dose of JAKAVI in PV is 10 mg given orally twice daily.

The recommended starting dose of JAKAVI in steroid refractory graft-versus-host disease (GvHD) is based on age (see Table 4-2).

Table 4-2 Starting doses in steroid refractory graft-versus-host disease (GvHD)

Age group	Starting dose
12 years old and above	10 mg orally twice daily
6 years to less than 12 years old	5 mg orally twice daily

These starting doses in steroid refractory graft-versus-host disease (GvHD) can be administered using the tablet for patients at or above 6 years old who can swallow tablets.

Dose modifications

Doses may be titrated based on safety and efficacy.

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

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

Treatment should be discontinued for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dL. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a differential white blood cell count.

Dose reductions should be considered if the platelet count decreases, during treatment as outlined in Table 4-3, with the goal of avoiding dose interruptions for thrombocytopenia.

Table 4-3 Dosing Recommendation for Thrombocytopenia in Myelofibrosis

	Dose at Time of Platelet Decline				
	25 mg twice daily	20 mg twice daily	15 mg twice daily	10 mg twice daily	5 mg twice daily
Platelet Count	New Dose				
100,000 to <125,000/mm^3	20 mg twice daily	15 mg twice daily	No change	No change	No change
75,000 to <100,000/mm^3	10 mg twice daily	10 mg twice daily	10 mg twice daily	No change	No change

50,000 to <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

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

Steroid refractory Graft-versus-host disease (SR GvHD)

Dose reductions and temporary interruptions of treatment may be needed in SR GvHD patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth-factors, anti-infective therapies and transfusions. One dose level reduction step is recommended (10 mg twice daily to 5 mg twice daily*;* 5 mg twice daily to 5 mg once daily). In patients who are unable to tolerate JAKAVI at the reduced dose level, treatment should be interrupted. Detailed dosing recommendations are provided in Table 4-4.

Table 4-4 Dosing recommendations for patients with thrombocytopenia, neutropenia, or elevated total bilirubin in patients with graft-versus- host disease

Laboratory Parameter	Dosing Recommendation
Platelet count < 20,000/mm^3	Reduce JAKAVI by one dose level. If platelet count ≥ 20.000/mm^3 within seven days, dose may be increased to initial dose level, otherwise maintain reduced dose.
Platelet count < 15,000/mm^3	Hold JAKAVI until platelet count ≥ 20,000/mm^3, then resume at one lower dose level.

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

Dose adjustment with concomitant strong CYP3A4 inhibitors or dual moderate CYP2C9/CYP3A4 inhibitors.

When JAKAVI is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes, (e.g. fluconazole) the unit dose of JAKAVI should be reduced by approximately 50 %, to be administered twice daily (see section 4.5). The concomitant use of JAKAVI with fluconazole doses greater than 200 mg daily should be avoided.

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

Special populations

Renal impairment

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

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

Pharmacokinetic/pharmacodynamic simulations based on available data in patients with end-stage renal disease (ESRD) suggest that the starting dose for MF patients on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis.

A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm^3 and 200,000/mm^3. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm^3. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis.

There are limited data to determine the best dosing options for SR GvHD patients with end stage renal disease (ESRD) on haemodialysis.

These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

Hepatic impairment

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

In SR GvHD patients with any hepatic impairment including liver GvHD, no starting dose modification is recommended (see section 5.1).

In patients with GvHD liver involvement and an increase of total bilirubin to > 3.0 x ULN, blood counts should be monitored more frequently for toxicity and a dose reduction by one dose level may be considered.

Elderly patients (≥ 65 years)

No additional dose adjustments are recommended for elderly patients.

Paediatric population

The safety and efficacy of JAKAVI in children and adolescents aged up to 18 years with MF and PV have not been established.

In paediatric patients (6 years of age and older) with SR GvHD, the safety and efficacy of JAKAVI have been established based on clinical studies (see section 4.8).

Treatment discontinuation

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

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

Method of administration

JAKAVI is to be taken orally, with or without food.

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

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy and lactation.
- Acute phase of serious infections.
- Acute hepatitis B infection or a history of hepatitis B infection not well controlled with appropriate treatment.
- Haemoglobin ≤ 8 g/dL.
- Platelet count ≤ 50,000 mm^3.
- Total neutrophil count ≤ 500 mm^3.
- Active or latent/dormant pulmonary or extrapulmonary tuberculosis.
- HIV infection.
- Presence of a basal cell and/or squamous cell carcinoma.
- Vaccination with a live attenuated bacterial or viral vaccine.
- Concomitant use with cytoreductive therapies or haematopoietic growth factors.

4.4 Special warnings and precautions for use

Infections, haematological abnormalities and malignancies listed in the contraindication section must first be treated until cured/resolved, improved, well controlled, reversed or in case of haematological abnormalities, improved with values outside the contraindication domain, before therapy with JAKAVI can be initiated.

If an infection, haematological abnormality or malignancy cannot be cured/resolved, improved, well controlled, reversed or in case of haematological abnormalities, improved with values outside the contraindication domain, those conditions remain contraindications to initiation of therapy with JAKAVI and other appropriate treatment options for treatment of the patient should be considered.

Myelosuppression

Treatment with JAKAVI may cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a differential white blood cell count, must be performed before initiating therapy with JAKAVI. Treatment should be discontinued in patients with platelet count less than 50,000/mm^3 or absolute neutrophil count less than 500/mm^3 (see section 4.2 and 4.3).

It has been observed that patients with low platelet counts (< 200,000/mm^3) at the start of therapy are more likely to develop thrombocytopenia during treatment.
Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding JAKAVI (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.
Patients with a haemoglobin level below 10.0 g/dL at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dL during treatment compared to patients with a higher baseline haemoglobin level (79.3 % versus 30.1 %). More frequent monitoring of haematology parameters and of clinical signs and symptoms of JAKAVI related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dL.

Neutropenia (absolute neutrophil count < 500) was generally reversible and was managed by temporarily withholding JAKAVI (see 4.2 and 4.8).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections 4.2 and 4.8).

Infections
Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with JAKAVI. Patients should be assessed for the risk of developing serious infections. Medical practitioners should carefully observe patients receiving JAKAVI for signs and symptoms of infections and initiate appropriate treatment promptly. Treatment with JAKAVI should not be started until active serious infections have resolved (see section 4.3).
Tuberculosis has been reported in patients receiving JAKAVI. Before starting treatment, patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as

applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised (see section 4.3).

Hepatitis B reactivation and/or 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 should be screened for hepatitis B infection before initiating treatment with JAKAVI. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines (see section 4.3).

Herpes zoster

Medical practitioners should educate patients about early signs and symptoms of herpes zoster, including extra cutaneous herpes zoster infections, advising that treatment should be sought as early as possible.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with JAKAVI treatment. Medical practitioners 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. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see section 4.3).

Lipid abnormalities/elevations

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

Special populations

Renal impairment

The starting dose of JAKAVI should be reduced in patients with severe renal impairment (CrCL < 30 mL/min). For patients with end stage renal disease on haemodialysis the starting dose for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. In SR GvHD patients with severe renal impairment, the starting dose of JAKAVI should be reduced by approximately 50 %. Additional dose modifications should be made with careful monitoring of safety and efficacy (see sections 4.2 and 5.2).

Hepatic impairment

The starting dose of JAKAVI should be reduced by approximately 50 % in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product (see sections 4.2 and 5.2).

Interactions

If JAKAVI is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the unit dose of JAKAVI should be reduced by approximately
50 %, to be administered twice daily (for monitoring frequency see sections 4.2 and 4.5).

The concomitant use of cytoreductive therapies or haematopoietic growth factors with JAKAVI has not been studied. The safety and efficacy of these co administrations are not known (see 4.3 and 4.5).

Withdrawal effects

Following interruption or discontinuation of JAKAVI, symptoms of MF may return over a period of approximately one week. There have been cases of patients discontinuing JAKAVI who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of JAKAVI contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of JAKAVI may be considered, although the utility of the tapering is unproven.

Excipients

JAKAVI contains lactose. Patients with rare hereditary problems of galactose intolerance (e.g.

galactosaemia), the Lapp lactase deficiency or glucose galactose malabsorption should not take JAKAVI.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

JAKAVI (ruxolitinib) is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicines inhibiting these enzymes can give rise to an increased ruxolitinib exposure.

Interactions resulting in dose reduction of JAKAVI

CYP3A4 inhibitors

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

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

When administering JAKAVI with strong CYP3A4 inhibitors the unit dose of JAKAVI should be reduced by approximately 50 %, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section 4.2).

Dual CYP2C9 and CYP3A4 inhibitors

In healthy subjects receiving fluconazole, a dual CYP2C9 and CYP3A4 inhibitor, as a single 400 mg dose followed by 200 mg once daily for seven days, there was a 232 % increase in the AUC of ruxolitinib.

50 % dose reduction should be considered when using medicines which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of JAKAVI with fluconazole doses greater than 200 mg daily.

Enzyme inducers

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

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section 4.2).

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

Other interactions to be considered affecting JAKAVI

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

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC that were higher by 8 % and 27 %, respectively, than with ruxolitinib alone.
No dose adjustment is recommended when JAKAVI is co-administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). However, patients should be closely monitored for cytopenias when initiating therapy with a moderate CYP3A4 inhibitor.

Effects of JAKAVI on other medicines

Substances transported by P-glycoprotein or other transporters
JAKAVI may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised.

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

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

efficacy of JAKAVI (see section 4.4).

Cytoreductive therapies

The concomitant use of cytoreductive therapies and JAKAVI has not been studied. The safety and efficacy of this co-administration is not known (see section 4.4).

Midazolam

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with ruxolitinib.

Oral contraceptives containing ethinyl-oestradiol and levonorgestrel

Another study in healthy subjects indicated that ruxolitinib does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of JAKAVI.

4.6 Fertility, pregnancy and lactation

Pregnancy

JAKAVI is contraindicated in pregnancy.

Ruxolitinib was embryotoxic and foetotoxic in animal studies (increases in post-implantation loss and reduced foetal weights) (see section 4.3).

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential should use effective contraception during the treatment with JAKAVI. Pregnancy should be excluded before initiation of treatment with JAKAVI. Pregnancy tests should be performed at regular intervals during treatment to exclude pregnancy.

Breastfeeding

Women on treatment with JAKAVI should not breastfeed their babies (see section 4.3).
In lactating rats, ruxolitinib and/or its metabolites are 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 breastmilk.

Fertility

There are no human data on the effect of JAKAVI on fertility. In animal studies, no effect on fertility was observed.

4.7 Effects on ability to drive and use machines

JAKAVI may influence the ability to drive and use machines. Patients should first ascertain how treatment of JAKAVI is affecting their mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgement and/or sound coordination and vision.
Adverse events such as dizziness, bleeding, anaemia, headache, infections and hypertension may influence their ability to drive and operate machines.
JAKAVI has no or negligible sedating effect. However, patients who experience dizziness after the intake of JAKAVI should refrain from driving or using machines.

4.8 Undesirable effects

Summary of safety profile

Myelofibrosis

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

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

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (83.8 %), thrombocytopenia (80.5 %), and neutropenia (20.8 %).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

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

The most frequent non-haematological laboratory abnormalities were increased alanine aminotransferase (ALT) (40.7 %), increased aspartate aminotransferase (AST) (31.5 %) and hypertriglyceridaemia (25.2 %). However, no CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed. Discontinuation due to adverse events, regardless of causality, was observed in 30.0 % of patients treated with ruxolitinib.

Polycythaemia vera

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

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

Haematological adverse reactions (any CTCAE grade) included anaemia (61.8 %) and thrombocytopenia (25.0 %) and neutropenia (5.3%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 2.9 % or 2.6 % of patients.

The most frequent non-haematological adverse reactions were weight gain (20.3 %), dizziness (19.4 %), and headache (17.9 %).
The most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as adverse reactions were increased alanine aminotransferase (43.3 %), increased aspartate aminotransferase (42.6 %), and hypercholesterolaemia (34.7 %). The majority were all CTCAE grade 1 and 2 with one CTCAE grade 4 increased aspartate aminotransferase event.
Discontinuation due to adverse events, regardless of causality, was observed in 19.4 % of patients treated with JAKAVI.

Acute graft-versus-host disease

The safety of JAKAVI in acute GvHD patients was evaluated in the phase 3 study REACH2 and

in the phase 2 study REACH4.

REACH2 included data from 201 patients ≥12 years of age, including patients initially randomised to JAKAVI (n = 152) and patients who received JAKAVI after crossing over from control treatment (n = 49). The median exposure upon which the ADR frequency categories were based was 8.9 weeks (range 0.3 to 66.1 weeks). In the pool of paediatric patients in REACH2 and REACH4, the median exposure was 16.7 weeks (range 1.1 to 48.9 weeks).

The most frequent ADRs (>50 %) in adult and adolescent patients in REACH2 were thrombocytopenia, anaemia, neutropenia, increased alanine aminotransferase (ALT), and increased aspartate aminotransferase (AST). The most frequent ADRs (>50 %) in the pool of paediatric patients in REACH2 and REACH4 were anaemia, neutropenia, increased ALT, hypercholesterolaemia and thrombocytopenia.

The most frequent haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH2 and in the pool of paediatric patients in REACH2 and REACH4 were thrombocytopenia (85.2 % and 55.1 %), anaemia (75.0 % and 70.8 %) and neutropenia (65.1 % and 70.0 %). Grade 3 anaemia was reported in 47.7 % of adult and adolescent patients in REACH2 and in 45.8 % of pooled paediatric patients in REACH2 and. Grade 3 and grade 4 thrombocytopenia were reported in 31.3 % and 47.7 % of adult and adolescent patients in REACH2 and in 14.6 % and 22.4 % of pooled paediatric patients in REACH2 and REACH4. Grade 3 and 4 neutropenia were reported in 17.9 % and 20.6 % of adult and adolescent patients in REACH2 and in 32.0 % and 22.0 % of pooled paediatric patients in REACH2 and REACH4, respectively.

The most frequent (>15 %) non-haematological ADRs in adult and adolescent patients in REACH2 and in the pool of paediatric patients in REACH2 and REACH4 were cytomegalovirus (CMV) infection (32.3 % and 31.4 %), sepsis (25.4 % and 9.8 %), urinary tract infections (UTI) (17.9 % and 9.8 %) hypertension (13.4 % and 17.6 %) and nausea (16.4 % and 3.9 %), respectively.

The three non-haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH2 and in the pool of paediatric patients in REACH2 and REACH4 were increased ALT (54.9 % and 63.3 %), increased AST (52.3 % and 50.0 %) and hypercholesterolaemia (49.2 % and 61.2 %), respectively. The majority were of grade 1 and grade 2, however grade 3 increased ALT was reported in 17.6 % of adult and adolescent patients in REACH2 and in 27.3 % of pooled of paediatric patients in REACH2 and REACH4.

Discontinuation due to AEs, regardless of causality, was observed in 29.4 % of adult and adolescent patients treated with JAKAVI in REACH2 and in 21.6 % of pooled paediatric patients in REACH 2 and REACH4.

Chronic graft-versus-host disease

The safety of JAKAVI in chronic GvHD patients was evaluated in the phase 3 study REACH3 and in the phase 2 study REACH5.

REACH3, included data from 226 patients ≥12 years of age, including patients initially randomised to JAKAVI (n = 165) and patients who received JAKAVI after crossing over from best available treatment (BAT) [n = 61]. The median exposure upon which the ADR frequency categories were based was 41.4 weeks (range 0.7 to 127.3 weeks). In the pool of paediatric

patients in REACH3 and REACH5, the median exposure was 57.1 weeks (range 2.1 to 155.4 weeks).

The most frequent ADRs (>50 %) in adult and adolescent patients in REACH3 were anaemia, hypercholesterolemia and increased AST. The most frequent ADRs (>50 %) in the pool of paediatric patients in REACH3 and REACH5 were neutropenia, hypercholesterolaemia, and increased ALT.

The most frequent-haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH3 and in the pool of paediatric patients in REACH3 and REACH5 were anaemia (68.6 % and 49.1 %), neutropenia (36.2 % and 59.3 %) and thrombocytopenia (34.4 % and 35.2 %). Grade 3 anaemia was reported in 14.8 % of adult and adolescent patients in REACH3 and in 17.0 % of pooled paediatric patients in REACH3 and REACH5. Grade 3 and 4 thrombocytopenia were reported in 5.9 % and 10.7 % of adult and adolescent patients in REACH3 and in 7.7 % and 11.1 % of pooled paediatric patients in REACH3 and REACH5. Grade 3 and grade 4 neutropenia were reported in 9.5 % and 6.7 % of adult and adolescent patients in REACH3 and in 17.3 % and 11.1 % of pooled paediatric patients in REACH3 and REACH5, respectively.

The most frequent (>10 %) non-haematological ADRs in adult and adolescent patients in REACH3 and in the pool of paediatric patients in REACH3 and REACH5 were hypertension (15.0 % and 14.5 %), and headache (10.2 % and 18.2 %), respectively.

The most frequent (>50 %) non-haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH3 and in the pool of paediatric patients in REACH3 and

REACH5 were hypercholesterolemia (52.3 % and 54.9 %), increased AST (52.2 % and 45.5 %) and increased ALT (43.1 % and 50.9 %). The majority were grade 1 and grade 2, however grade 3 laboratory abnormalities increased ALT and increased AST were reported in 4.7 % and 3.1 % of adult and adolescent patients in REACH3 and in 14.9 % and 11.5 % of pooled paediatric patients in REACH3 and REACH5.

Discontinuation due to AEs, regardless of causality, was observed in 18.1 % of adult and adolescent patients treated with JAKAVI in REACH3 and in 14.5 % of pooled paediatric patients in REACH3 and REACH5.

Tabulated summary of adverse reactions

In the clinical study programme, the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4 = life threatening.

Adverse drug reactions from clinical studies in MF and PV are listed in Table 4.8-1. ADRs from clinical trials in acute and chronic GvHD are listed in Table 4.8-2 and Table 4.8-3. All ADRs are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 4.8-1 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE, RESPONSE 2) in myelofibrosis and polycythemia vera.

Adverse drug reaction	**Frequency category for MF patients**	**Frequency category for PV patients**
	Long-term follow-up data Week 256: COMFORT-I Week 256: COMFORT-II	**Long-term follow-up data Week 256: RESPONSE Week 156: RESPONSE-2**
Infections and infestations		
Urinary tract infections[1]	Very common	Very common
Pneumonia	Very common	Common
Herpes zoster[1]	Very common	Very common
Sepsis	Common	-
Tuberculosis[2]	Uncommon	-
Blood and lymphatic system disorders		
Anaemia[2]		
CTCAE[c] grade 4 (< 6.5 g/dL)	Very common	Uncommon
CTCAE[c] grade 3 (< 8.0 – 6.5 g/dL)	Very common	Common
Any CTCAE[c] grade	Very common	Very common
Thrombocytopenia[2]		
CTCAE[c] grade 4	Common	Uncommon

(< 25,000/mm^3)		
CTCAE[c] grade 3 (50,000 – 25,000/mm^3)	Very common	Common
Any CTCAE[c] grade	Very common	Very common
Neutropenia[2]		
CTCAE[c] grade 4 (< 500/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (< 1,000 – 500/mm^3)	Common	Uncommon
Any CTCAE[c] grade	Very common	Common
Pancytopenia[2, 3]	Common	Common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and/or haematoma and other bleeding)	Very common	Very common
Intracranial bleeding	Common	-
Gastrointestinal bleeding	Common	-
Bruising and/or haematoma	Very common	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Common	Very common
Metabolism and nutrition disorders		
Weight gain[1]	Very common	Very common

Hypercholesterolaemia[2] Any CTCAE[c] grade	Very common	Very common
Hypertriglyceridaemia[2] CTCAE[c] grade 1	Very common	Very common
Nervous system disorders		
Dizziness[1]	Very common	Very common
Headache[1]	Very common	Very common
Gastrointestinal disorders		
Flatulence[1]	Common	Common
Constipation[1]	Very common	Very common
Skin and subcutaneous tissue disorders		
Bruising	Very common	Very common
Hepatobiliary disorders		
Increased alanine aminotransferase[2]		
CTCAE[c] grade 3 (> 5x – 20 x ULN)	Common	Common
Any CTCAE[c] grade	Very common	Very common
Increased aspartate aminotransferase[2]		
Any CTCAE[c] grade	Very common	Very common
Vascular disorders		
Hypertension[1]	Very common	Very common

[1] Frequency is based on new or worsened laboratory abnormalities compared to baseline

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

[4] Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

Table 4.8-2 ADRs reported in clinical studies in acute graft-versus-host disease

	Adult and adolescent patients (REACH2) (N=201)			**Paediatric patients (REACH2 and REACH4) (N=51)**		
ADR	Frequency category	All grades (%)	CTCAE[3] grade 3 / 4 (%)	Frequency category	All grades (%)	CTCAE[3] grade 3 / 4 (%)
Infections and infestations						
CMV infections	Very common	32.3	10.9 / 0.5	Very common	31.4	5.9 / 0
Sepsis[4]	Very common	25.4	4.0 / 17.9	Common	9.8	2.0 / 5.9
Urinary tract infections	Very common	17.9	6.0 / 0.5	Common	9.8	2.0 / 0
Blood and lymphatic system disorders						
Thrombocytopenia[1]	Very common	85.2	31.3 / 47.7	Very common	55.1	14.6 / 22.4
Anaemia[1]	Very common	75.0	47.7 / NA	Very common	70.8	45.8 / NA
Neutropenia[1]	Very common	65.1	17.9 / 20.6	Very common	70.0	32.0 / 22.0
Pancytopenia[1,2]	Very common	32.8	NA	Very common	25.5	NA
Metabolism and nutrition disorders						

Hypercholesterolaemia[1]	Very common	49.2	3.3 / 5.9	Very common	61.2	0 / 0
Nervous system disorders						
Headache	Common	8.5	0.5 / 0	Common	5.9	0 / 0
Vascular disorders						
Hypertension	Very common	13.4	5.5 / 0	Very common	17.6	15.7 / 0
Gastrointestinal disorders						
Nausea	Very common	16.4	0.5 / 0	Common	3.9	0 / 0
Hepatobiliary disorders						
Increased ALT[1]	Very common	54.9	17.6 / 1.5	Very common	63.3	27.3 / 0
Increased AST[1]	Very common	52.3	7.8 / 0	Very common	50.0	6.1 / 0

[1] Frequency is based on new or worsened laboratory abnormalities compared to baseline.

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

[3] CTCAE Version 4.03.

[4] Grade 4 sepsis includes 16 (8%) grade 4 events and 20 (10%) grade 5 events in REACH2. There were no grade 5 events in the paediatric pool.

NA: Not applicable. No CTCAE grade defined based on laboratory values.

Table 4.8-3 ADRs reported in clinical studies in chronic graft-versus-host disease

	Adult and adolescent patients (REACH3) (N=226)			**Paediatric patients (REACH3 and REACH5) (N=55)**		
ADR	Frequency category	All grades (%)	CTCAE[2] grade 3 / 4 (%)	Frequency category	All grades (%)	CTCAE[2] grade 3 / 4 (%)
Infections and infestations						
Urinary tract infections	Common	9.3	1.3 / 0	Common	5.5	1.8 / 0
BK virus infections	Common	4.9	0.4 / 0	Common	1.8	0 / 0
Blood and lymphatic system disorders						
Anaemia[1]	Very common	68.6	14.8 / NA	Very common	49.1	17.0 / NA
Neutropenia[1]	Very common	36.2	9.5 / 6.7	Very common	59.3	17.3 /11.1
Thrombocytopenia[1]	Very common	34.4	5.9 / 10.7	Very common	35.2	7.7 / 11.1
Metabolism and nutrition disorders						
Hypercholesterolaemia[1]	Very common	52.3	5.5 / 0.5	Very common	54.9	4.1 / 5.9
Weight gain	Common	3.5	0 / 0	Common	5.5	3.6 / 0

Nervous system disorders						
Headache	Very common	10.2	1.3 / 0	Very common	18.2	1.8 / 0
Vascular disorders						
Hypertension	Very common	15.0	5.3 / 0	Very common	14.5	3.6 / 0
Gastrointestinal disorders						
Increased lipase[1]	Very common	35.9	9.5 / 0.4	Very common	20.4	3.8 /1.9
Increased amylase[1]	Very common	32.4	4.2 / 2.7	Very common	25.9	9.4 / 0
Constipation	Common	6.6	0 / 0	Common	5.5	0 / 0
Hepatobiliary disorders						
Increased AST[1]	Very common	52.2	3.1 / 0.9	Very common	45.5	11.5 / 0
Increased ALT[1]	Very common	43.1	4.7 / 0.9	Very common	50.9	14.9 / 3.6
Musculoskeletal and connective tissue disorders						
Increased blood CPK[1]	Very common	31.1	1.0 / 1.4	Very common	22.6	0 / 0
Renal and urinary disorders						
Increased blood creatinine[1]	Very common	38.4	1.3 / 0	Common	7.3	0 / 0

[1] *Frequency is based on new or worsened laboratory abnormalities compared to baseline.*

[2] *CTCAE Version 4.03.*

NA: Not applicable. No CTCAE grade defined based on laboratory values.

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

The following ADRs are derived from post-marketing experience with JAKAVI-via spontaneous case reports and in the literature. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore characterized as ‘not known’.

Infections and infestations: Tuberculosis (PV patients)

Description of selected adverse reactions

Anaemia

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

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

In the randomised, placebo-controlled study COMFORT I 60.6 % of JAKAVI-treated MF patients and 37.7 % of placebo treated MF patients received red blood cell transfusions during

randomised 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.

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (40.8 % versus 82.4 %). In the PV population, the CTCAE grade 3 and grade 4 events were reported in 2.7 %, while in the MF patients the frequency was 42.5 %.

In the phase 3 acute (REACH2) and chronic GvHD (REACH3) studies, respectively, (all grades) was reported in 75.0 % and 68.6 % of adult and adolescent patients; anaemia CTCAE Grade 3 was reported in 47.7 % and 14.8 % of adult and adolescent patients. In the pool of paediatric patients with acute (REACH2 and REACH4) and chronic (REACH3 and REACH5) GvHD, anaemia (all grades) was reported in 70.8 % and 49.1 % of patients, respectively. CTCAE grade 3 was reported in 45.8 % and 17.0 % of acute and chronic GvHD patients, respectively.

Thrombocytopenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or grade 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 randomised period, platelet transfusions were administered to 4.7 % of patients receiving ruxolitinib and to 4.0 % of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7 % of patients receiving ruxolitinib 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 ruxolitinib had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2 % versus 38.5 %).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (16.8 %) patients compared to MF (69.8 %) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (2.7 %) than in MF (11.6 %) patients.

In the phase 3 acute GvHD study in adult and adolescent patients (REACH2), grade 3 and grade 4 thrombocytopenia was observed in 31.3 % and 47.7 % of patients, respectively. In the phase 3 chronic GvHD study grade 3 and grade 4 thrombocytopenia was lower (5.9 % and 10.7 %) than in acute GvHD. The frequency of grade 3 (14.6 %) and grade 4 (22.4 %) thrombocytopenia in the pool of paediatric patients with acute GvHD in REACH2 and REACH4 was lower than in adult and adolescent patients in REACH2. In the pool of paediatric patients with chronic GvHD in REACH3 and REACH5, grade 3 and grade 4 thrombocytopenia was lower (7.7 % and 11.1 %) than in paediatric patients with acute GvHD in REACH2 and REACH4.

Neutropenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or grade 4 neutropenia, the median time to onset was 12 weeks. During the randomised period, dose holding or reductions due to neutropenia were reported in 1.0 % of patients, and 0.3 % of patients discontinued treatment because of neutropenia.

In the randomised period of the pivotal study in PV patients, neutropenia was reported in three patients (1.6 %) of which one patient developed CTCAE grade 4 neutropenia. During the long-term follow-up, 2 patients reported CTCAE grade 4 neutropenia.

In the phase 3 acute GvHD study (REACH2), grade 3 and grade 4 neutropenia was observed in 17.9 % and 20.6 % of adult and adolescent patients, respectively. In the phase 3 chronic GvHD study REACH3, grade 3 and grade 4 neutropenia was lower (9.5 % and 6.7 %) than in acute GvHD. In paediatric patients with acute GvHD in REACH2 and REACH4, the frequency of grade 3 and grade 4 neutropenia was 32.0 % and 22.0 %, respectively. In paediatric patients with chronic GvHD in REACH3 and REACH5 the frequency of grade 3 and grade 4 neutropenia was 17.3 % and 11.1 %, respectively.

Bleeding

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

In the comparative period of phase 3 studies in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 16.8 % of

patients treated with ruxolitinib, 15.3 % of patients receiving best available therapy in RESPONSE study and 12.0 % of patients receiving best available therapy in RESPONSE 2 study.

Bruising and/or haematoma was reported in 10.3 % of patients treated with ruxolitinib, 8.1 % of patients receiving best available therapy in RESPONSE study and 2.7 % of patients receiving best available therapy in RESPONSE 2 study. No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving ruxolitinib. One patient treated with ruxolitinib experienced a grade 3 bleeding event (post procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post procedural haemorrhage, gingival bleeding) were reported in 8.7 % of patients treated with ruxolitinib, 6.3 % of patients treated with best available therapy in RESPONSE study and 6.7 % of patients treated with best available therapy in RESPONSE 2 study.

Infections

In the phase 3 pivotal studies in MF, grade 3 or grade 4 urinary tract infection was reported in 1.0 % of patients, herpes zoster in 4.3 % and tuberculosis in 1.0 %. In phase 3 clinical studies sepsis was reported in 3.0 % of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time.

In the randomised period of the pivotal study in PV patients, one (0.5 %) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was similar in PV (4.3 %) patients and MF (4.0 %) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

During the long-term follow-up, urinary tract infection of any grade was observed in 21.4 % and 11.8 % of MF and PV patients, respectively and herpes zoster of any grade was observed in 19.7 % and 14.7 % of MF and PV patients, respectively.

In the phase 3 acute GvHD study REACH2, grade 3 and grade 4 CMV infections were reported in 10.9 % and 0.5 % of patients, respectively. CMV infection with organ involvement was seen in very few patients; CMV colitis, CMV enteritis and CMV gastrointestinal infection of any grade were reported in four, two and one patients, respectively.
Sepsis events including septic shock of any grade were reported in 25.4 % of adult and adolescent patients in REACH2.

UTI and sepsis were reported with lower frequency in the pool of paediatric patients with acute GvHD in REACH2 and REACH4 (9.8 %, each) compared with adult and adolescent patients in REACH2.

In the phase 3 chronic GvHD study REACH3, Grade 3 urinary tract infections and BK virus infections were reported in 1.3 % and 0.4 % of patients, respectively.

In the pool of paediatric patients in REACH3 and REACH5 with chronic GvHD, UTI (all grades) were reported in 5.5 % (grade 3, 1.8 %) of patients and BK virus infection was reported in 1.8 % (no grade ≥3) of patients.

Increased systolic blood pressure
In the phase 3 pivotal clinical studies in MF 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 (MF patients) the mean increase from baseline in systolic BP was 0 to 2 mmHg on ruxolitinib versus a decrease of 2 to 5 mmHg in the placebo arm. In COMFORT II mean values showed little difference between the ruxolitinib treated and the control treated MF patients.

In the randomised period of the pivotal study in PV patients, the mean systolic blood pressure increased by 0.65 mmHg in the ruxolitinib arm versus a decrease of 2 mmHg in the BAT arm.

Post-marketing reported side effects

Progressive multifocal leukoencephalopathy (PML), and non -melanoma skin cancers (basal cell carcinoma, squamous cell carcinoma and Merkel cell carcinoma), and pancytopenia have been reported with the use of JAKAVI (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the, Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA-website and via email to: patientsafety.sacg@novartis.com.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity.

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, anaemia and thrombocytopenia. Appropriate symptomatic and supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of JAKAVI (ruxolitinib).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EJ01

Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2. These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

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

Ruxolitinib inhibits JAK STAT signalling and cell proliferation of cytokine dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.

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

Pharmacodynamic effects

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects, MF patients and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and MF patients, indicating no accumulation of either parent or active metabolites. Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFα, IL 6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

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

5.2 Pharmacokinetic properties

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, 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 human mass balance study, oral absorption of ruxolitinib, as ruxolitinib or metabolites formed under first pass, is 95 % or greater. 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) on dosing with a high fat meal.

Distribution

The mean volume of distribution at steady state ($V_{D,ss}$) is approximately 75 litres in MF and PV patients. The mean $V_{D,ss}$ in adolescent and adult acute GvHD patients is 67.5 L whereas in chronic GvHD patients it is 60.9 L. The mean $V_{D,ss}$ is approximately 30 L in paediatric patients with acute or chronic GvHD and with a body surface area (BSA) below 1. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins *in vitro* is approximately 97 %, mostly to albumin. A whole-body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood brain barrier.

Biotransformation

Ruxolitinib is mainly metabolised by CYP3A4 (>50 %), with additional contribution from CYP2C9. Parent compound is the predominant entity in human plasma, representing approximately 60 % of the drug related material in circulation. Two major and active metabolites are present in plasma 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 contributes to 18 % of the overall pharmacodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19,

CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on *in vitro* studies. *In vitro* data indicate that ruxolitinib may inhibit P-gp and BCRP.

Elimination

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half-life of ruxolitinib is approximately 3 hours. Following a single oral dose of [^{14}C] labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74 % of radioactivity excreted in urine and 22 % via faeces. Unchanged parent substance accounted for less than 1 % of the excreted total radioactivity.

Linearity/non-linearity

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

Special populations

Effects of age, gender or race

Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race.

Population pharmacokinetics

In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 L/h in women and 22.1 L/h in men, with 39 % inter subject variability in MF patients. Clearance was 12.7 L/h in PV patients, with a 42 % inter subject variability and no relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in PV patients. Clearance was 10.4 L/h in adult and adolescent patients with acute

GvHD and 7.8 L/h in adolescent and adult patients with chronic GvHD, with 48.7 % inter-subject variability. In paediatric patients with acute or chronic GvHD and with a BSA below 1, clearance was between 6.5 L/h and 7 L/h. No relationship was apparent between oral clearance and gender, patient age or race, based on a PopPK evaluation in GvHD patients. At a dose of 10 mg twice daily, exposure was increased in GvHD patients with a low body surface area (BSA). In subjects with a BSA of 1 m^2, 1.25 m^2 and 1.5 m^2, the predicted mean exposure (AUC) was respectively 31 %, 22 % and 12 % higher than the typical adult (1.79 m^2).

Renal impairment

Renal function was determined using both Modification of Diet in Renal Disease (MDRD) and urinary creatinine. Following a single ruxolitinib dose of 25 mg, the exposure of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and were most markedly increased in the subjects with severe renal impairment. It is unknown whether the increased metabolite exposure is of safety concern. A dose modification is recommended in patients with severe renal impairment and end stage renal disease (see section 4.2). Dosing only on dialysis days reduces the metabolite exposure, but also the pharmacodynamic effect, especially on the days between dialysis.

Hepatic impairment

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87 %, 28 % and 65 %, respectively, compared to patients with normal hepatic function. There was no clear relationship between AUC and 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 of approximately 50 % is recommended for patients with hepatic impairment (see section 4.2).

Paediatric populations

The pharmacokinetics of ruxolitinib in paediatric patients with MF and PV < 18 years of age have not been established (see section 5.1, “Paediatric population”).

As in adult patients with GvHD, ruxolitinib was rapidly absorbed after oral administration in paediatric patients with GvHD. Dosing in children between 6 and 11 years at 5 mg twice daily achieved comparable exposure to a dose of 10 mg twice daily in adolescents and adults, confirming the exposure matching approach implemented as part of the extrapolation assumption. In REACH4 and REACH5, ruxolitinib has not been evaluated in paediatric patients with acute or chronic GvHD below the age of 2 years, therefore physiologically-based pharmacokinetic modeling which accounts for age related aspects in younger patients has been used to predict the exposures in these patients, based on the data from patients aged 6 years and older.

Based on a pooled population pharmacokinetic analysis in paediatric patients with acute or chronic GvHD, clearance of ruxolitinib decreased with decreasing BSA. After correcting for the BSA effect, other demographic factors such as age, body weight and body mass index did not have clinically significant effects on the exposure of ruxolitinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose, microcrystalline
- Magnesium stearate
- Silica, colloidal anhydrous
- Sodium starch glycolate (Type A)
- Povidone K30
- Hydroxypropylcellulose 300 to 600 cps
- Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture.

Store in the original package.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister packs containing 14 or 56 tablets or multipacks containing 168 (3 packs of 56) tablets.

Not all pack sizes or types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

Tel. (011) 347 6600

8. REGISTRATION NUMBER(S)

Jakavi 5 mg tablets: 48/34/0109

Jakavi 10 mg tablets: 52/34/0781

Jakavi 15 mg tablets: 48/34/0110

Jakavi 20 mg tablets: 48/34/0111

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Jakavi 5, 15 and 20 mg tablets: 20 April 2017

Jakavi 10 mg tablets: 19 May 2020

10. DATE OF REVISION OF THE TEXT

14 May 2026

Namibia	
5 mg: 19/32.2/0037	NS2
15 mg: 19/32.2/0038	NS2
20 mg: 19/32.2/0039	NS2