

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Jakavi 5 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 71.45 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

Round 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.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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.

### 4.2 Posology and method of administration

Jakavi treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

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

Complete blood count, including a white blood cell count differential, 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 is 15 mg twice daily for patients with a platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup> and 20 mg twice daily for patients with a platelet count of >200,000/mm<sup>3</sup>. There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm<sup>3</sup> and <100,000/mm<sup>3</sup>. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

##### Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm<sup>3</sup> or absolute neutrophil counts less than 500/mm<sup>3</sup>. After recovery of platelet and neutrophil 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 white blood cell count differential.

Dose reductions should be considered if the platelet count decreases below 100,000/mm<sup>3</sup>, with the goal of avoiding dose interruptions for thrombocytopenia.

If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased by a maximum of 5 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.

The maximum dose of Jakavi is 25 mg twice daily.

#### Dose adjustment with concomitant strong CYP3A4 inhibitors or fluconazole

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (see section 4.5).

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 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.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Available data in this population suggest that the starting dose for patients with ESRD on haemodialysis is a single dose of 15 mg or 20 mg, to be administered after haemodialysis has been completed and only on the day of haemodialysis. A single dose of 15 mg is for patients with platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup> or a single dose of 20 mg for patients with platelet count of >200,000/mm<sup>3</sup>. Subsequent doses should be administered once daily on haemodialysis days following each dialysis session. Dosing only on dialysis days, applying a dialysis frequency of 3 times a week, is estimated to result in a low STAT3 inhibitory effect 24-48 hours post dose (see section 5.2). Other dosing regimens may be more suitable from an efficacy perspective. However, due to increased metabolite exposure and lack of knowledge on the potential safety consequences of these exposures, dose modification 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 white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

##### Elderly patients (≥65 years)

No additional dose adjustments are recommended for elderly patients.

### *Paediatric population*

The safety and efficacy of Jakavi in children aged up to 18 years have not been established. No data are available (see section 5.1).

### Treatment discontinuation

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

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

### 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.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

## **4.4 Special warnings and precautions for use**

### Myelosuppression

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

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

Thrombocytopenia 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 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 sections 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

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and 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 section 4.8).

### Herpes zoster

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

### Special populations

#### *Renal impairment*

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts (see section 4.2). Subsequent doses (single administration) should be administered on haemodialysis days following each dialysis session. 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 section 4.5).

### Withdrawal effects

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

### Excipients

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

## Interactions resulting in dose reduction of ruxolitinib

### 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 ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

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

### Dual CYP2C9 and CYP3A4 inhibitors

On the basis of *in silico* modelling 50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole).

### Enzyme inducers

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

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section 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 Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near  $E_{max}$ . It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

### Other interactions to be considered affecting ruxolitinib

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

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

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

### Effects of ruxolitinib on other medicinal products

#### Oral contraceptives

There is no interaction study with oral contraceptives.

#### Substances metabolised by CYP3A4

It cannot be excluded that ruxolitinib inhibits CYP3A4 in the intestine. Increased systemic exposure may be obtained for substances which are metabolised by CYP3A4, and particularly those that undergo extensive intestinal metabolism. Safety monitoring of orally administered CYP3A4 metabolised substances is advised when combined with ruxolitinib. The interaction is likely to be minimised if the time between co-administrations is kept as long as possible.

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

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

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be 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).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy and contraception in females

There are no data from the use of Jakavi in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, the use of Jakavi during pregnancy is contraindicated (see section 4.3). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 5.3).

#### Breast-feeding

Jakavi must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

#### Fertility

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

### **4.7 Effects on ability to drive and use 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 the safety profile

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

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (15.6%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.0%) and headache (13.9%).

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

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

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 (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).



**Table 1 Percentage of patients with adverse drug reactions in clinical studies \***

Adverse drug reaction	Ruxolitinib – myelofibrosis patients N=301*		
	All CTCAE grades <sup>c</sup> (%)	CTCAE grade 3/4 <sup>c</sup> (%)	Frequency category
<b>Infections and infestations</b>			
Urinary tract infections <sup>a,d</sup>	12.3	1.0	Very common
Herpes zoster <sup>a,d</sup>	4.3	0.3	Common
<b>Blood and lymphatic system disorders<sup>b,d</sup></b>			
Anaemia	82.4	42.5	Very common
Thrombocytopenia	69.8	11.3	Very common
Neutropenia	15.6	6.6	Very common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	32.6	4.7	Very common
Intracranial bleeding	1.0	1.0	Common
Gastrointestinal bleeding	5.0	1.3	Common
Bruising	21.3	0.3	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	13.3	2.3	Very common
<b>Metabolism and nutrition disorders</b>			
Weight gain <sup>a</sup>	10.0	1.3	Very common
Hypercholesterolaemia <sup>b</sup>	16.6	0	Very common
<b>Nervous system disorders</b>			
Dizziness <sup>a</sup>	15.0	0.3	Very common
Headache <sup>a</sup>	13.9	0.5	Very common
<b>Gastrointestinal disorders</b>			
Flatulence <sup>a</sup>	2.9	0	Common
<b>Hepatobiliary disorders</b>			
Raised alanine aminotransferase <sup>b</sup>	26.9	1.3	Very common
Raised aspartate aminotransferase <sup>b</sup>	19.3	0	Very common
* Myelofibrosis patients randomised to and treated with ruxolitinib from the phase 3 pivotal COMFORT-I and COMFORT-II studies			
<sup>a</sup> Frequency is based on adverse event data.			
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.			
- ADRs reported are on treatment or up to 28 days post treatment end date.			
<sup>b</sup> 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.			
<sup>c</sup> Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening			
<sup>d</sup> These ADRs are discussed in the text.			

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

## Description of selected adverse drug reactions

### *Anaemia*

In phase 3 clinical studies, 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 Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

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

### *Thrombocytopenia*

In the phase 3 clinical studies, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm<sup>3</sup> was 14 days. 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<sup>3</sup> to 200,000/mm<sup>3</sup> before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm<sup>3</sup> (64.2% versus 38.5%).

### *Neutropenia*

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

### *Bleeding*

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

### *Infections*

In the phase 3 pivotal studies grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%.

### *Increased systolic blood pressure*

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

## 4.9 Overdose

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 supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE18

#### Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC<sub>50</sub> values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Myelofibrosis is a myeloproliferative neoplasm 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. Myelofibrosis patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status.

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<sub>50</sub> ranging from 80-320 nM.

#### Pharmacodynamic effects

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF $\alpha$ , IL-6 and CRP in subjects with myelofibrosis were decreased following treatment with ruxolitinib. Myelofibrosis patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time.

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.

#### Clinical efficacy and safety

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with myelofibrosis (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate-2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group (IWG) Consensus Criteria. The starting dose of Jakavi was based on platelet count.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. Patients were given Jakavi or matching

placebo. The primary efficacy endpoint was proportion of subjects achieving  $\geq 35\%$  reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

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

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

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

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

**Table 2 Percentage of patients with  $\geq 35\%$  reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)**

	COMFORT-I		COMFORT-II	
	Jakavi (N=155)	Placebo (N=153)	Jakavi (N=144)	Best available therapy (N=72)
Time points	Week 24		Week 48	
Number (%) of subjects with spleen volume reduced by $\geq 35\%$	65 (41.9)	1 (0.7)	41 (28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the Jakavi group achieved  $\geq 35\%$  reduction from baseline in spleen volume (Table 2) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythaemia vera myelofibrosis, post-essential thrombocythaemia myelofibrosis).

**Table 3 Percentage of patients with  $\geq 35\%$  reduction from baseline in spleen volume by JAK mutation status (safety set)**

	COMFORT-I				COMFORT-II			
	Jakavi		Placebo		Jakavi		Best available therapy	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by $\geq 35\%$	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

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

Jakavi improves myelofibrosis-associated symptoms and quality of life in patients with myelofibrosis. In COMFORT-I symptoms of myelofibrosis were captured using the modified MFSAF diary v2.0 as an electronic diary which subjects completed daily. 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-square test).

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, 13 out of 155 patients (8.4%) died in the Jakavi group and 24 out of 154 patients (15.6%) died in the placebo group. In COMFORT-II, 13 out of 146 patients (8.9%) died in the Jakavi group and 5 out of 73 patients (6.8%) died in the best available therapy group.

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jakavi in all subsets of the paediatric population for the treatment of myelofibrosis (see section 4.2 for information on paediatric use).

## **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 apparent volume of distribution at steady state is 53-65 litres in myelofibrosis patients. 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 hepatic 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 intestinal CYP3A4, 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 [<sup>14</sup>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*

In healthy subjects, no significant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in myelofibrosis patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability.

#### *Paediatric population*

The safety and effectiveness of Jakavi in paediatric patients have not been established (see section 5.1, "Paediatric population").

#### *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).

### **5.3 Preclinical safety data**

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

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

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

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years  
After first-opening: 1 month

### **6.4 Special precautions for storage**

Do not store above 30°C.

### **6.5 Nature and contents of container**

HDPE bottle with induction seal and child-resistant closure containing 60 tablets.

### **6.6 Special precautions for disposal**

No special requirements.

**7.     MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

**8.     MARKETING AUTHORISATION NUMBER(S)**

**9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10.    DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>



## 1. NAME OF THE MEDICINAL PRODUCT

Jakavi 15 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 214.35 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

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.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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.

### 4.2 Posology and method of administration

Jakavi treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

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

Complete blood count, including a white blood cell count differential, 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 is 15 mg twice daily for patients with a platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup> and 20 mg twice daily for patients with a platelet count of >200,000/mm<sup>3</sup>. There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm<sup>3</sup> and <100,000/mm<sup>3</sup>. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

##### Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm<sup>3</sup> or absolute neutrophil counts less than 500/mm<sup>3</sup>. After recovery of platelet and neutrophil 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 white blood cell count differential.

Dose reductions should be considered if the platelet count decreases below 100,000/mm<sup>3</sup>, with the goal of avoiding dose interruptions for thrombocytopenia.

If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased by a maximum of 5 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.

The maximum dose of Jakavi is 25 mg twice daily.

#### Dose adjustment with concomitant strong CYP3A4 inhibitors or fluconazole

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (see section 4.5).

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 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.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Available data in this population suggest that the starting dose for patients with ESRD on haemodialysis is a single dose of 15 mg or 20 mg, to be administered after haemodialysis has been completed and only on the day of haemodialysis. A single dose of 15 mg is for patients with platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup> or a single dose of 20 mg for patients with platelet count of >200,000/mm<sup>3</sup>. Subsequent doses should be administered once daily on haemodialysis days following each dialysis session. Dosing only on dialysis days, applying a dialysis frequency of 3 times a week, is estimated to result in a low STAT3 inhibitory effect 24-48 hours post dose (see section 5.2). Other dosing regimens may be more suitable from an efficacy perspective. However, due to increased metabolite exposure and lack of knowledge on the potential safety consequences of these exposures, dose modification 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 white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

##### Elderly patients (≥65 years)

No additional dose adjustments are recommended for elderly patients.

### *Paediatric population*

The safety and efficacy of Jakavi in children aged up to 18 years have not been established. No data are available (see section 5.1).

### Treatment discontinuation

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

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

### 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.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

## **4.4 Special warnings and precautions for use**

### Myelosuppression

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

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

Thrombocytopenia 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 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 sections 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

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and 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 section 4.8).

### Herpes zoster

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

### Special populations

#### *Renal impairment*

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts (see section 4.2). Subsequent doses (single administration) should be administered on haemodialysis days following each dialysis session. 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 section 4.5).

### Withdrawal effects

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

### Excipients

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

## Interactions resulting in dose reduction of ruxolitinib

### 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 ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

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

### Dual CYP2C9 and CYP3A4 inhibitors

On the basis of *in silico* modelling 50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole).

### Enzyme inducers

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

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section 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 Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near  $E_{max}$ . It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

### Other interactions to be considered affecting ruxolitinib

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

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

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

### Effects of ruxolitinib on other medicinal products

#### Oral contraceptives

There is no interaction study with oral contraceptives.

#### Substances metabolised by CYP3A4

It cannot be excluded that ruxolitinib inhibits CYP3A4 in the intestine. Increased systemic exposure may be obtained for substances which are metabolised by CYP3A4, and particularly those that undergo extensive intestinal metabolism. Safety monitoring of orally administered CYP3A4 metabolised substances is advised when combined with ruxolitinib. The interaction is likely to be minimised if the time between co-administrations is kept as long as possible.

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

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

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be 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).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy and contraception in females

There are no data from the use of Jakavi in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, the use of Jakavi during pregnancy is contraindicated (see section 4.3). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 5.3).

#### Breast-feeding

Jakavi must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

#### Fertility

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

### **4.7 Effects on ability to drive and use 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 the safety profile

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

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (15.6%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.0%) and headache (13.9%).

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

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

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 (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

**Table 1 Percentage of patients with adverse drug reactions in clinical studies \***

Adverse drug reaction	Ruxolitinib – myelofibrosis patients N=301*		
	All CTCAE grades <sup>c</sup> (%)	CTCAE grade 3/4 <sup>c</sup> (%)	Frequency category
<b>Infections and infestations</b>			
Urinary tract infections <sup>a,d</sup>	12.3	1.0	Very common
Herpes zoster <sup>a,d</sup>	4.3	0.3	Common
<b>Blood and lymphatic system disorders<sup>b,d</sup></b>			
Anaemia	82.4	42.5	Very common
Thrombocytopenia	69.8	11.3	Very common
Neutropenia	15.6	6.6	Very common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	32.6	4.7	Very common
Intracranial bleeding	1.0	1.0	Common
Gastrointestinal bleeding	5.0	1.3	Common
Bruising	21.3	0.3	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	13.3	2.3	Very common
<b>Metabolism and nutrition disorders</b>			
Weight gain <sup>a</sup>	10.0	1.3	Very common
Hypercholesterolaemia <sup>b</sup>	16.6	0	Very common
<b>Nervous system disorders</b>			
Dizziness <sup>a</sup>	15.0	0.3	Very common
Headache <sup>a</sup>	13.9	0.5	Very common
<b>Gastrointestinal disorders</b>			
Flatulence <sup>a</sup>	2.9	0	Common
<b>Hepatobiliary disorders</b>			
Raised alanine aminotransferase <sup>b</sup>	26.9	1.3	Very common
Raised aspartate aminotransferase <sup>b</sup>	19.3	0	Very common
* Myelofibrosis patients randomised to and treated with ruxolitinib from the phase 3 pivotal COMFORT-I and COMFORT-II studies			
<sup>a</sup> Frequency is based on adverse event data.			
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.			
- ADRs reported are on treatment or up to 28 days post treatment end date.			
<sup>b</sup> 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.			
<sup>c</sup> Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening			
<sup>d</sup> These ADRs are discussed in the text.			

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



## Description of selected adverse drug reactions

### *Anaemia*

In phase 3 clinical studies, 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 Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

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

### *Thrombocytopenia*

In the phase 3 clinical studies, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm<sup>3</sup> was 14 days. 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<sup>3</sup> to 200,000/mm<sup>3</sup> before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm<sup>3</sup> (64.2% versus 38.5%).

### *Neutropenia*

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

### *Bleeding*

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

### *Infections*

In the phase 3 pivotal studies grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%.

### *Increased systolic blood pressure*

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

## 4.9 Overdose

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 supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE18

#### Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC<sub>50</sub> values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Myelofibrosis is a myeloproliferative neoplasm 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. Myelofibrosis patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status.

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<sub>50</sub> ranging from 80-320 nM.

#### Pharmacodynamic effects

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF $\alpha$ , IL-6 and CRP in subjects with myelofibrosis were decreased following treatment with ruxolitinib. Myelofibrosis patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time.

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.

#### Clinical efficacy and safety

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with myelofibrosis (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate-2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group (IWG) Consensus Criteria. The starting dose of Jakavi was based on platelet count.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. Patients were given Jakavi or matching

placebo. The primary efficacy endpoint was proportion of subjects achieving  $\geq 35\%$  reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

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

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

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

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

**Table 2 Percentage of patients with  $\geq 35\%$  reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)**

	COMFORT-I		COMFORT-II	
	Jakavi (N=155)	Placebo (N=153)	Jakavi (N=144)	Best available therapy (N=72)
Time points	Week 24		Week 48	
Number (%) of subjects with spleen volume reduced by $\geq 35\%$	65 (41.9)	1 (0.7)	41 (28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the Jakavi group achieved  $\geq 35\%$  reduction from baseline in spleen volume (Table 2) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythaemia vera myelofibrosis, post-essential thrombocythaemia myelofibrosis).

**Table 3 Percentage of patients with  $\geq 35\%$  reduction from baseline in spleen volume by JAK mutation status (safety set)**

	COMFORT-I				COMFORT-II			
	Jakavi		Placebo		Jakavi		Best available therapy	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by $\geq 35\%$	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

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

Jakavi improves myelofibrosis-associated symptoms and quality of life in patients with myelofibrosis. In COMFORT-I symptoms of myelofibrosis were captured using the modified MFSAF diary v2.0 as an electronic diary which subjects completed daily. 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-square test).

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, 13 out of 155 patients (8.4%) died in the Jakavi group and 24 out of 154 patients (15.6%) died in the placebo group. In COMFORT-II, 13 out of 146 patients (8.9%) died in the Jakavi group and 5 out of 73 patients (6.8%) died in the best available therapy group.

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jakavi in all subsets of the paediatric population for the treatment of myelofibrosis (see section 4.2 for information on paediatric use).

## **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 apparent volume of distribution at steady state is 53-65 litres in myelofibrosis patients. 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 hepatic 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 intestinal CYP3A4, 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 [<sup>14</sup>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*

In healthy subjects, no significant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in myelofibrosis patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability.

#### *Paediatric population*

The safety and effectiveness of Jakavi in paediatric patients have not been established (see section 5.1, "Paediatric population").

#### *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).

### **5.3 Preclinical safety data**

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

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

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

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years  
After first-opening: 1 month

### **6.4 Special precautions for storage**

Do not store above 30°C.

### **6.5 Nature and contents of container**

HDPE bottle with induction seal and child-resistant closure containing 60 tablets.

### **6.6 Special precautions for disposal**

No special requirements.

**7.     MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

**8.     MARKETING AUTHORISATION NUMBER(S)**

**9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10.    DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## 1. NAME OF THE MEDICINAL PRODUCT

Jakavi 20 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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

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.

### 4.2 Posology and method of administration

Jakavi treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

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

Complete blood count, including a white blood cell count differential, 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 is 15 mg twice daily for patients with a platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup> and 20 mg twice daily for patients with a platelet count of >200,000/mm<sup>3</sup>. There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm<sup>3</sup> and <100,000/mm<sup>3</sup>. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

##### Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm<sup>3</sup> or absolute neutrophil counts less than 500/mm<sup>3</sup>. After recovery of platelet and neutrophil 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 white blood cell count differential.



Dose reductions should be considered if the platelet count decreases below 100,000/mm<sup>3</sup>, with the goal of avoiding dose interruptions for thrombocytopenia.

If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased by a maximum of 5 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.

The maximum dose of Jakavi is 25 mg twice daily.

#### Dose adjustment with concomitant strong CYP3A4 inhibitors or fluconazole

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (see section 4.5).

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 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.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Available data in this population suggest that the starting dose for patients with ESRD on haemodialysis is a single dose of 15 mg or 20 mg, to be administered after haemodialysis has been completed and only on the day of haemodialysis. A single dose of 15 mg is for patients with platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup> or a single dose of 20 mg for patients with platelet count of >200,000/mm<sup>3</sup>. Subsequent doses should be administered once daily on haemodialysis days following each dialysis session. Dosing only on dialysis days, applying a dialysis frequency of 3 times a week, is estimated to result in a low STAT3 inhibitory effect 24-48 hours post dose (see section 5.2). Other dosing regimens may be more suitable from an efficacy perspective. However, due to increased metabolite exposure and lack of knowledge on the potential safety consequences of these exposures, dose modification 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 white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

##### Elderly patients (≥65 years)

No additional dose adjustments are recommended for elderly patients.

### *Paediatric population*

The safety and efficacy of Jakavi in children aged up to 18 years have not been established. No data are available (see section 5.1).

### Treatment discontinuation

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

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

### 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.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

## **4.4 Special warnings and precautions for use**

### Myelosuppression

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

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

Thrombocytopenia 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 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 sections 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

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and 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 section 4.8).

### Herpes zoster

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

### Special populations

#### *Renal impairment*

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts (see section 4.2). Subsequent doses (single administration) should be administered on haemodialysis days following each dialysis session. 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 section 4.5).

### Withdrawal effects

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

### Excipients

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

## Interactions resulting in dose reduction of ruxolitinib

### 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 ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

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

### Dual CYP2C9 and CYP3A4 inhibitors

On the basis of *in silico* modelling 50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole).

### Enzyme inducers

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

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section 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 Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near  $E_{max}$ . It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

### Other interactions to be considered affecting ruxolitinib

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

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

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

### Effects of ruxolitinib on other medicinal products

#### Oral contraceptives

There is no interaction study with oral contraceptives.

#### Substances metabolised by CYP3A4

It cannot be excluded that ruxolitinib inhibits CYP3A4 in the intestine. Increased systemic exposure may be obtained for substances which are metabolised by CYP3A4, and particularly those that undergo extensive intestinal metabolism. Safety monitoring of orally administered CYP3A4 metabolised substances is advised when combined with ruxolitinib. The interaction is likely to be minimised if the time between co-administrations is kept as long as possible.

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

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

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be 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).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy and contraception in females

There are no data from the use of Jakavi in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, the use of Jakavi during pregnancy is contraindicated (see section 4.3). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 5.3).

#### Breast-feeding

Jakavi must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

#### Fertility

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

### **4.7 Effects on ability to drive and use 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 the safety profile

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

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (15.6%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.0%) and headache (13.9%).

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

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

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 (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

**Table 1 Percentage of patients with adverse drug reactions in clinical studies \***

Adverse drug reaction	Ruxolitinib – myelofibrosis patients N=301*		
	All CTCAE grades <sup>c</sup> (%)	CTCAE grade 3/4 <sup>c</sup> (%)	Frequency category
<b>Infections and infestations</b>			
Urinary tract infections <sup>a,d</sup>	12.3	1.0	Very common
Herpes zoster <sup>a,d</sup>	4.3	0.3	Common
<b>Blood and lymphatic system disorders<sup>b,d</sup></b>			
Anaemia	82.4	42.5	Very common
Thrombocytopenia	69.8	11.3	Very common
Neutropenia	15.6	6.6	Very common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	32.6	4.7	Very common
Intracranial bleeding	1.0	1.0	Common
Gastrointestinal bleeding	5.0	1.3	Common
Bruising	21.3	0.3	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	13.3	2.3	Very common
<b>Metabolism and nutrition disorders</b>			
Weight gain <sup>a</sup>	10.0	1.3	Very common
Hypercholesterolaemia <sup>b</sup>	16.6	0	Very common
<b>Nervous system disorders</b>			
Dizziness <sup>a</sup>	15.0	0.3	Very common
Headache <sup>a</sup>	13.9	0.5	Very common
<b>Gastrointestinal disorders</b>			
Flatulence <sup>a</sup>	2.9	0	Common
<b>Hepatobiliary disorders</b>			
Raised alanine aminotransferase <sup>b</sup>	26.9	1.3	Very common
Raised aspartate aminotransferase <sup>b</sup>	19.3	0	Very common
* Myelofibrosis patients randomised to and treated with ruxolitinib from the phase 3 pivotal COMFORT-I and COMFORT-II studies			
<sup>a</sup> Frequency is based on adverse event data.			
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.			
- ADRs reported are on treatment or up to 28 days post treatment end date.			
<sup>b</sup> 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.			
<sup>c</sup> Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening			
<sup>d</sup> These ADRs are discussed in the text.			

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

## Description of selected adverse drug reactions

### *Anaemia*

In phase 3 clinical studies, 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 Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

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

### *Thrombocytopenia*

In the phase 3 clinical studies, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm<sup>3</sup> was 14 days. 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<sup>3</sup> to 200,000/mm<sup>3</sup> before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm<sup>3</sup> (64.2% versus 38.5%).

### *Neutropenia*

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

### *Bleeding*

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

### *Infections*

In the phase 3 pivotal studies grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%.

### *Increased systolic blood pressure*

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



## 4.9 Overdose

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 supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE18

#### Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC<sub>50</sub> values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Myelofibrosis is a myeloproliferative neoplasm 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. Myelofibrosis patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status.

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<sub>50</sub> ranging from 80-320 nM.

#### Pharmacodynamic effects

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF $\alpha$ , IL-6 and CRP in subjects with myelofibrosis were decreased following treatment with ruxolitinib. Myelofibrosis patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time.

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.

#### Clinical efficacy and safety

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with myelofibrosis (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate-2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group (IWG) Consensus Criteria. The starting dose of Jakavi was based on platelet count.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. Patients were given Jakavi or matching

placebo. The primary efficacy endpoint was proportion of subjects achieving  $\geq 35\%$  reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

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

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

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

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

**Table 2 Percentage of patients with  $\geq 35\%$  reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)**

	COMFORT-I		COMFORT-II	
	Jakavi (N=155)	Placebo (N=153)	Jakavi (N=144)	Best available therapy (N=72)
Time points	Week 24		Week 48	
Number (%) of subjects with spleen volume reduced by $\geq 35\%$	65 (41.9)	1 (0.7)	41 (28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the Jakavi group achieved  $\geq 35\%$  reduction from baseline in spleen volume (Table 2) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythaemia vera myelofibrosis, post-essential thrombocythaemia myelofibrosis).

**Table 3 Percentage of patients with  $\geq 35\%$  reduction from baseline in spleen volume by JAK mutation status (safety set)**

	COMFORT-I				COMFORT-II			
	Jakavi		Placebo		Jakavi		Best available therapy	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by $\geq 35\%$	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

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

Jakavi improves myelofibrosis-associated symptoms and quality of life in patients with myelofibrosis. In COMFORT-I symptoms of myelofibrosis were captured using the modified MFSAF diary v2.0 as an electronic diary which subjects completed daily. 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-square test).

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, 13 out of 155 patients (8.4%) died in the Jakavi group and 24 out of 154 patients (15.6%) died in the placebo group. In COMFORT-II, 13 out of 146 patients (8.9%) died in the Jakavi group and 5 out of 73 patients (6.8%) died in the best available therapy group.

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jakavi in all subsets of the paediatric population for the treatment of myelofibrosis (see section 4.2 for information on paediatric use).

## **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 apparent volume of distribution at steady state is 53-65 litres in myelofibrosis patients. 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 hepatic 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 intestinal CYP3A4, 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 [<sup>14</sup>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*

In healthy subjects, no significant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in myelofibrosis patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability.

#### *Paediatric population*

The safety and effectiveness of Jakavi in paediatric patients have not been established (see section 5.1, "Paediatric population").

#### *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).

### **5.3 Preclinical safety data**

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

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

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

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years  
After first-opening: 1 month

### **6.4 Special precautions for storage**

Do not store above 30°C.

### **6.5 Nature and contents of container**

HDPE bottle with induction seal and child-resistant closure containing 60 tablets.

### **6.6 Special precautions for disposal**

No special requirements.

**7.     MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

**8.     MARKETING AUTHORISATION NUMBER(S)**

**9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10.    DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

### Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH  
Roonstrasse 25  
D-90429 Nürnberg  
Germany

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

### Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

### Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Follow-up efficacy and safety data from the extension phase of studies INCB 18424-351 and INC424A2352 including data on the time related endpoints (overall survival, progression free survival and leukaemia free survival) should be provided annually.	Annually to coincide with the anniversary of European birth date



**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

Jakavi 5 mg tablets  
Ruxolitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 5 mg ruxolitinib (as phosphate).

**3. LIST OF EXCIPIENTS**

Contains lactose (see leaflet for further information).

**4. PHARMACEUTICAL FORM AND CONTENTS**

Tablets

60 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[carton only]  
Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Jakavi 5 mg [carton only]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

Jakavi 15 mg tablets  
Ruxolitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 15 mg ruxolitinib (as phosphate).

**3. LIST OF EXCIPIENTS**

Contains lactose (see leaflet for further information).

**4. PHARMACEUTICAL FORM AND CONTENTS**

Tablets

60 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[carton only]  
Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Jakavi 15 mg [carton only]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**CARTON AND BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

Jakavi 20 mg tablets  
Ruxolitinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 20 mg ruxolitinib (as phosphate).

**3. LIST OF EXCIPIENTS**

Contains lactose (see leaflet for further information).

**4. PHARMACEUTICAL FORM AND CONTENTS**

Tablets

60 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[carton only]  
Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Jakavi 20 mg [carton only]



**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

**Jakavi 5 mg tablets**  
**Jakavi 15 mg tablets**  
**Jakavi 20 mg tablets**  
ruxolitinib

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

### **What is in this leaflet**

1. What Jakavi is and what it is used for
2. What you need to know before you take Jakavi
3. How to take Jakavi
4. Possible side effects
5. How to store Jakavi
6. Contents of the pack and other information

### **1. What Jakavi is and what it is used for**

Jakavi contains the active substance ruxolitinib.

Jakavi is used to treat adult patients with an enlarged spleen or with symptoms related to myelofibrosis, a rare form of blood cancer.

#### **How Jakavi works**

Enlargement of the spleen is one of the characteristics of myelofibrosis. Myelofibrosis is a disorder of the bone marrow, in which the marrow is replaced by scar tissue. The abnormal marrow can no longer produce enough normal blood cells and as a result the spleen becomes significantly enlarged. By blocking the action of certain enzymes (called Janus Associated Kinases), Jakavi can reduce the size of the spleen in patients with myelofibrosis and relieve symptoms such as fever, night sweats, bone pain and weight loss. Jakavi can help reduce the risk of serious blood or vascular complications.

If you have any questions about how Jakavi works or why this medicine has been prescribed for you, ask your doctor.

### **2. What you need to know before you take Jakavi**

Follow all the doctor's instructions carefully. They may differ from the general information contained in this leaflet.

#### **Do not take Jakavi**

- if you are allergic to ruxolitinib or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or breast-feeding.

If either of the above applies to you, tell your doctor who will then decide whether you should start treatment with Jakavi.

## **Warnings and precautions**

Talk to your doctor or pharmacist before taking Jakavi

- if you have any infections. It may be necessary to treat your infection before starting Jakavi.
- if you have any kidney problems. Your doctor may need to prescribe a different dose of Jakavi.
- if you have or have ever had any liver problems. Your doctor may need to prescribe a different dose of Jakavi.
- if you are taking other medicines (see section “Other medicines and Jakavi”).

Talk to your doctor or pharmacist during your treatment with Jakavi

- if you experience unexpected bruising and/or bleeding, unusual tiredness, shortness of breath during exercise or at rest, unusually pale skin, or frequent infections (these are signs of blood disorders).
- if you experience fever, chills or other symptoms of infections.
- if you develop painful skin rash with blisters (these are signs of shingles).

## Blood tests

Before you start treatment with Jakavi, your doctor will perform blood tests to determine the best starting dose for you. You will need to have further blood tests during treatment so that your doctor can monitor the amount of blood cells (white cells, red cells and platelets) in your body and assess how you are responding to the treatment and whether Jakavi is having an unwanted effect on these cells. Your doctor may need to adjust the dose or stop treatment.

## Stopping Jakavi

When you stop taking Jakavi, the myelofibrosis symptoms may come back. Your doctor may want to gradually reduce the amount of Jakavi taken each day, before stopping it completely.

## **Children and adolescents**

Do not give this medicine to children or adolescents aged below 18 years because the use of Jakavi in children has not been studied.

## **Other medicines and Jakavi**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is particularly important that you mention any of the following medicines containing any of the following active substances, as your doctor may need to adjust the Jakavi dose for you.

The following may increase the risk of side effects with Jakavi:

- Some medicines used to treat infections. These include medicines used to treat fungal diseases (such as ketoconazole, itraconazole, posaconazole, fluconazole and voriconazole), medicines used to treat certain types of bacterial infections (antibiotics such as clarithromycin, telithromycin, ciprofloxacin, or erythromycin), medicines to treat viral infections, including HIV infection/AIDS (such as apranavir, atazanavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir), medicines to treat hepatitis C (boceprevir, telaprevir).
- Nefazodone, a medicine to treat depression.
- Mibefradil or diltiazem, medicines to treat hypertension and chronic angina pectoris.
- Cimetidine, a medicine to treat heartburn.

The following may reduce the effectiveness of Jakavi:

- Avasimibe, a medicine to treat heart disease.
- Phenytoin, carbamazepine or phenobarbital and other anti-epileptics used to stop seizures or fits.
- Rifabutin or rifampicin, medicines used to treat tuberculosis (TB).
- St. John's wort (*Hypericum perforatum*), a herbal product used to treat depression.

**While you are taking Jakavi** you should never start a new medicine without checking first with the doctor who prescribed Jakavi. This includes prescription medicines, non-prescription medicines and herbal or alternative medicines.

### **Pregnancy and breast-feeding**

Do not take Jakavi during pregnancy. Talk to your doctor about how to take appropriate measures to avoid becoming pregnant during your treatment with Jakavi.

Do not breast-feed while taking Jakavi. Tell your doctor if you are breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

### **Driving and using machines**

If you experience dizziness after taking Jakavi, do not drive or use machines.

### **Jakavi contains lactose**

Jakavi contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## **3. How to take Jakavi**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The dose of Jakavi depends on the patient's blood cell count. Your doctor will measure the amount of blood cells in your body and find the best dose for you, particularly if you have liver or kidney problems.

- The recommended starting dose is 15 mg twice daily or 20 mg twice daily, depending on your blood cell count.
- The maximum dose is 25 mg twice daily.

Your doctor will always tell you exactly how many Jakavi tablets to take.

During the treatment your doctor may recommend a lower or higher dose to you if the results of blood tests show that this is necessary, if you have problems with your liver or kidneys, or if you also need treatment with certain other medicines.

If you receive dialysis, take one single dose of Jakavi on dialysis days, after the dialysis has been completed. Your doctor will tell you how many tablets to take for each dose.

You should take Jakavi every day at the same time, either with or without food.

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.

If you experience certain side effects (e.g. blood disorders), your doctor might need to change the amount of Jakavi you have to take or tell you to stop taking Jakavi for a while.

**If you take more Jakavi than you should**

If you accidentally take more Jakavi than your doctor prescribed, contact your doctor or pharmacist immediately.

**If you forget to take Jakavi**

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

**If you stop taking Jakavi**

If you interrupt your treatment with Jakavi your myelofibrosis-related symptoms may come back. Therefore, you should not stop taking Jakavi without discussing it with your doctor.

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

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most of the side effects of Jakavi are mild to moderate and will generally disappear after a few days to a few weeks of treatment.

Tell your doctor immediately if you experience any of the following side effects. Some are very common (may affect more than 1 in 10 people), some are common (may affect up to 1 in 10 people):

- any sign of bleeding in the brain, such as sudden altered level of consciousness, persistent headache, numbness, tingling, weakness or paralysis (common)
- any sign of bleeding in the stomach or intestine, such as passing black or bloodstained stools, or vomiting blood (common)
- unexpected bruising and/or bleeding, unusual tiredness, shortness of breath during exercise or at rest, unusually pale skin, or frequent infections (possible symptoms of blood disorders) (very common)
- painful skin rash with blisters (possible symptoms of shingles (*herpes zoster*)) (common)
- fever, chills or other symptoms of infections (very common)
- low level of red blood cells (*anaemia*), low level of white blood cells (*neutropenia*) or low level of platelets (*thrombocytopenia*) (very common)

Other side effects with Jakavi

Very common:

- high level of cholesterol
- abnormal liver function test results
- dizziness
- headache
- urinary tract infections
- weight gain

Common:

- frequently passing wind (*flatulence*)

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

## **5. How to store Jakavi**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label. Use within 1 month after opening the bottle.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Jakavi contains**

- The active substance of Jakavi is ruxolitinib.
- Each 5 mg Jakavi tablet contains 5 mg of ruxolitinib.
- Each 15 mg Jakavi tablet contains 15 mg of ruxolitinib.
- Each 20 mg Jakavi tablet contains 20 mg of ruxolitinib.
- The other ingredients are: microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, sodium starch glycolate, povidone, hydroxypropylcellulose, lactose monohydrate.

### **What Jakavi looks like and contents of the pack**

Jakavi 5 mg tablets are white to almost white round tablets with “NVR” debossed on one side and “L5” debossed on the other side.

Jakavi 15 mg tablets are white to almost white oval tablets with “NVR” debossed on one side and “L15” debossed on the other side.

Jakavi 20 mg tablets are white to almost white elongated tablets with “NVR” debossed on one side and “L20” debossed on the other side.

Jakavi tablets are packed in bottles. Each bottle contains 60 tablets.

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### **Manufacturer**

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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>