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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Polycythaemia vera (PV)
Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

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 in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm³ and 200,000/mm³ and 20 mg twice daily for patients with a platelet count of >200,000/mm³. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm³ and <100,000/mm³. 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/mm³ or absolute neutrophil counts less than 500/mm³. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential.

Dose reductions should be considered if the platelet count decreases below 100,000/mm³, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

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

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

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 for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.
There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm³ and 200,000/mm³. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm³. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

**Hepatic impairment**

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a 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.

**Older people (≥65 years)**

No additional dose adjustments are recommended for older people.

**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/mm³ or absolute neutrophil count less than 500/mm³ (see section 4.2).

It has been observed that patients with low platelet counts (<200,000/mm³) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see 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. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. 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).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Herpes zoster
Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.
Progressive multifocal leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

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

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 for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. 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 MF may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of Jakavi contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered, although the utility of the tapering is unproven.

Excipients
Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, 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\textsubscript{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\textsubscript{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\textsubscript{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**

*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).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

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 safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

Myelofibrosis
In the randomised period of the two pivotal studies, COMFORT-I and COMFORT-II, the median duration of exposure to Jakavi was 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of 301 patients, 111 (36.9%) had a baseline platelet count of between 100,000/mm³ and 200,000/mm³ and 190 (63.1%) had a baseline platelet count of >200,000/mm³.

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

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

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

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3-year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

Polycythaemia vera
The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%.
The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Table 1 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE)**

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Frequency category for MF patients</th>
<th>Frequency category for PV patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Herpes zoster⁵</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Tuberculosis⁶</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia⁷</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CTCAE⁸ grade 4 (&lt;6.5 g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE⁸ grade 3 (&lt;8.0 – 6.5 g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Any CTCAE⁸ grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Thrombocytopenia⁹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE⁸ grade 4 (&lt;25,000/mm³)</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE⁸ grade 3 (50,000 – 25,000/mm³)</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Any CTCAE⁸ grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Condition Description</td>
<td>Frequency</td>
<td>Grade</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>Neutropenia[^6]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE[^5] grade 4 (&lt;=500/mm[^3])</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>CTCAE[^5] grade 3 (500 – 1,000/mm[^3])</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Any CTCAE[^5] grade</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Bruising</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain[^a]</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Hypercholesterolaemia[^b]</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>CTCAE[^5] grade 1 and 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridaemia[^b]</td>
<td>-</td>
<td>Very common</td>
</tr>
<tr>
<td>CTCAE[^5] grade 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness[^a]</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Headache[^a]</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence[^a]</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Constipation[^a]</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised alanine aminotransferase[^b]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE[^5] grade 3 (500 – 1,000/mm[^3])</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Any CTCAE[^5] grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Raised aspartate aminotransferase[^b]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CTCAE[^5] grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension[^a]</td>
<td>-</td>
<td>Very common</td>
</tr>
</tbody>
</table>

[^a]: 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.

[^b]: 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.

[^c]: Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening

[^d]: These ADRs are discussed in the text.

[^e]: Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)
Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

**Description of selected adverse drug reactions**

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

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

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

*Thrombocytopenia*
In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm$^3$ was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm$^3$ to 200,000/mm$^3$ before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm$^3$ (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

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

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.

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

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

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

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

**Increased systolic blood pressure**
In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 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 MF patients.

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

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 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\textsubscript{50} 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 and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

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

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF\alpha, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

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

Clinical efficacy and safety

Myelofibrosis
Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (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 or high risk 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. 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, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (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. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

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

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

<table>
<thead>
<tr>
<th>Time points</th>
<th>COMFORT-I (N=155)</th>
<th>COMFORT-II (N=144)</th>
<th>Best available therapy (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of subjects with spleen volume reduced by ≥35%</td>
<td>65 (41.9)</td>
<td>1 (0.7)</td>
<td>41 (28.5)</td>
</tr>
<tr>
<td>95% confidence intervals</td>
<td>34.1, 50.1</td>
<td>0, 3.6</td>
<td>21.3, 36.6</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

A significantly higher proportion of patients in the Jakavi group achieved ≥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 ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

<table>
<thead>
<tr>
<th>JAK mutation status</th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jakavi (N=113)</td>
<td>Placebo (N=40)</td>
</tr>
<tr>
<td>Positive</td>
<td>54 (47.8)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>11 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.
In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group (p<0.0001 using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo (p<0.0001).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythemia vera and post essential thrombocythemia subgroups.

Polycythemia vera
A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the Jakavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 1). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib treatment at Week 32 or after, limiting the comparison between the two arms after Week 32.
Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT (p=0.0028) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT. (p<0.0001).

Figure 1  Patients achieving the primary endpoint and components of the primary endpoint at week 32

Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).

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 MF (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 mean volume of distribution at steady state is approximately 75 litres in MF and PV 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 CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on in vitro studies. In vitro data indicate that ruxolitinib may inhibit P-gp and BCRP.

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

Linearity/non-linearity
Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations
Effects of age, gender or race
Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in PV patients.

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 $C_{\text{max}}$) 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

Blisters
2 years

Bottles
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

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

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

Not all pack sizes or types may be marketed.

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 AUTHOURISATION NUMBER(S)

EU/1/12/773/001
EU/1/12/773/004-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.08.2012

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
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

Jakavi 10 mg tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 10 mg ruxolitinib (as phosphate).

**Excipient with known effect:**
Each tablet contains 142.90 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Tablet.

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

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

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

**Polycythaemia vera (PV)**
Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

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 in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm$^3$ and 200,000/mm$^3$ and 20 mg twice daily for patients with a platelet count of >200,000/mm$^3$. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

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

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

Dose reductions should be considered if the platelet count decreases below 100,000/mm$^3$, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

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

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

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 for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.
There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm$^3$ and 200,000/mm$^3$. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm$^3$. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

**Hepatic impairment**

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a 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.

**Older people (≥65 years)**

No additional dose adjustments are recommended for older people.

**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/mm³ or absolute neutrophil count less than 500/mm³ (see section 4.2).

It has been observed that patients with low platelet counts (<200,000/mm³) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see 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. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. 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).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

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

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

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

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 for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. 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 MF may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of Jakavi contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered, although the utility of the tapering is unproven.

Excipients

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, 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, neflinavir, 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\text{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\text{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, cimetidin)*

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C\text{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**

*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).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

### 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 safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

Myelofibrosis
In the randomised period of the two pivotal studies, COMFORT-I and COMFORT-II, the median duration of exposure to Jakavi was 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of 301 patients, 111 (36.9%) had a baseline platelet count of between 100,000/mm³ and 200,000/mm³ and 190 (63.1%) had a baseline platelet count of >200,000/mm³.

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

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

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

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3-year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

Polycythaemia vera
The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%. 
The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Frequency category for MF patients</th>
<th>Frequency category for PV patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Herpes zoster&lt;sup&gt;ad&lt;/sup&gt;</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Tuberculosis&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CTCAE&lt;sup&gt;c&lt;/sup&gt; grade 4 (&lt;6.5 g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE&lt;sup&gt;c&lt;/sup&gt; grade 3 (&lt;8.0 – 6.5 g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Any CTCAE&lt;sup&gt;c&lt;/sup&gt; grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Thrombocytopenia&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE&lt;sup&gt;e&lt;/sup&gt; grade 4 (&lt;25,000/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE&lt;sup&gt;e&lt;/sup&gt; grade 3 (50,000 – 25,000/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Any CTCAE&lt;sup&gt;e&lt;/sup&gt; grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>Neutropenia(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE(^c) grade 4 ((&lt;500/\text{mm}^3))</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>CTCAE(^c) grade 3 ((&lt;1,000 – 500/\text{mm}^3))</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Any CTCAE(^c) grade</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain(^a)</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Hypercholesterolaemia(^b) CTCAE(^c) grade 1 and 2</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Hypertriglyceridaemia(^b) CTCAE(^c) grade 1</td>
<td>-</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness(^a)</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Headache(^a)</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence(^a)</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Constipation(^a)</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised alanine aminotransferase(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE(^c) grade 3 ((&gt;5x – 20x \text{ULN}))</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Any CTCAE(^c) grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Raised aspartate aminotransferase(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CTCAE(^c) grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension(^d)</td>
<td>-</td>
<td>Very common</td>
</tr>
</tbody>
</table>

\(^a\) 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.

\(^b\) 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.

\(^c\) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening

\(^d\) These ADRs are discussed in the text.

\(^e\) Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)
Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

**Description of selected adverse drug reactions**

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

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

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

**Thrombocytopenia**
In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm\(^3\) was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm\(^3\) to 200,000/mm\(^3\) before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm\(^3\) (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

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

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.
Bleeding
In the phase 3 pivotal studies in MF bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to Jakavi and 23.2% of patients exposed to the reference treatments (placebo or best available therapy). The frequency of grade 3-4 events was similar for patients treated with Jakavi or reference treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%). Bruising events were more frequently reported in patients taking Jakavi compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to Jakavi and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to Jakavi compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

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

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

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

Increased systolic blood pressure
In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 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 MF patients.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.
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

Pharmacoerapeutic 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 (IC₅₀ 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 and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC₅₀ ranging from 80-320 nM.

**Pharmacodynamic effects**

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFα, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

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

**Clinical efficacy and safety**

**Myelofibrosis**

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (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 or high risk 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. The primary efficacy endpoint was proportion of subjects achieving ≥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 ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (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. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

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

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

<table>
<thead>
<tr>
<th>Time points</th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jakavi (N=155)</td>
<td>Placebo (N=153)</td>
</tr>
<tr>
<td>Number (%) of subjects with spleen volume reduced by ≥35%</td>
<td>65 (41.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>95% confidence intervals</td>
<td>34.1, 50.1</td>
<td>0, 3.6</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
A significantly higher proportion of patients in the Jakavi group achieved ≥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 ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

<table>
<thead>
<tr>
<th>JAK mutation status</th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jakavi</td>
<td>Placebo</td>
</tr>
<tr>
<td>Positive (N=113) n (%)</td>
<td>54 (47.8)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>Negative (N=40) n (%)</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group (p<0.0001 using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo (p<0.0001).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythaemia vera and post essential thrombocythaemia subgroups.

Polycythaemia vera
A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.
The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the Jakavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 1). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib treatment at Week 32 or after, limiting the comparison between the two arms after Week 32.

Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT (p=0.0028) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT.(p<0.0001).

Figure 1  Patients achieving the primary endpoint and components of the primary endpoint at week 32

Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).
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 MF (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 ($C_{\text{max}}$) 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

Distribution
The mean volume of distribution at steady state is approximately 75 litres in MF and PV 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 CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on in vitro studies. In vitro data indicate that ruxolitinib may inhibit P-gp and BCRP.

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

Linearity/non-linearity
Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations
Effects of age, gender or race
Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race based on a population pharmacokinetic evaluation in PV patients.
**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\text{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

**Blisters**
2 years

**Bottles**
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

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

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

Not all pack sizes or types may be marketed.

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)
EU/1/12/773/013-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23.08.2012

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
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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**

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

**Polycythaemia vera (PV)**
Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

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 in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm$^3$ and 200,000/mm$^3$ and 20 mg twice daily for patients with a platelet count of >200,000/mm$^3$. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

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

**Dose modifications**

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

Dose reductions should be considered if the platelet count decreases below 100,000/mm$^3$, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

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

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

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 for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.
There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm$^3$ and 200,000/mm$^3$. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm$^3$. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

**Hepatic impairment**
In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a 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.

**Older people (≥65 years)**
No additional dose adjustments are recommended for older people.

**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$^3$ or absolute neutrophil count less than 500/mm$^3$ (see section 4.2).

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

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see 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. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. 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).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

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

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

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

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 for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. 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 MF may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of Jakavi contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered, although the utility of the tapering is unproven.

Excipients

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, 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, neflinavir, 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 $C_{\text{max}}$ 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 $E_{\text{max}}$. 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, ampicillin, 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 $C_{\text{max}}$ 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

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).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

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 safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

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

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

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

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

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3-year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

**Polycythaemia vera**
The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%.
The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE)

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Frequency category for MF patients</th>
<th>Frequency category for PV patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Herpes zoster&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Tuberculosis&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CTCAE grade 4 (≤6.5g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE grade 3 (6.0 – 6.5g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Any CTCAE grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Thrombocytopenia&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE grade 4 (≤25,000/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>CTCAE grade 3 (25,000 – 50,000/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Any CTCAE grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Neutropenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CTCAE&lt;sup&gt;c&lt;/sup&gt; grade 4 (&lt;500/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>CTCAE&lt;sup&gt;c&lt;/sup&gt; grade 3 (&lt;1,000 – 500/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Any CTCAE&lt;sup&gt;c&lt;/sup&gt; grade</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Weight gain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia&lt;sup&gt;b&lt;/sup&gt; CTCAE&lt;sup&gt;c&lt;/sup&gt; grade 1 and 2</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridaemia&lt;sup&gt;b&lt;/sup&gt; CTCAE&lt;sup&gt;c&lt;/sup&gt; grade 1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dizziness&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Headache&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Flatulence&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Constipation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Raised alanine aminotransferase&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CTCAE&lt;sup&gt;c&lt;/sup&gt; grade 3 (&lt;5x – 20 x ULN)</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Any CTCAE&lt;sup&gt;c&lt;/sup&gt; grade</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Raised aspartate aminotransferase&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Any CTCAE&lt;sup&gt;c&lt;/sup&gt; grade</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hypertension&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Very common</td>
<td></td>
</tr>
</tbody>
</table>

<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.

<sup>e</sup> Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)
Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

**Description of selected adverse drug reactions**

**Anaemia**

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

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

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

**Thrombocytopenia**

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm$^3$ was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm$^3$ to 200,000/mm$^3$ before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm$^3$ (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

**Neutropenia**

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

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.
**Bleeding**

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

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

**Infections**

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

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

**Increased systolic blood pressure**

In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 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 MF patients.

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

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**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\textsubscript{50} 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 and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

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

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF\alpha, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

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

Clinical efficacy and safety

Myelofibrosis
Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (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 or high risk 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. The primary efficacy endpoint was proportion of subjects achieving ≥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 ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (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. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

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

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

<table>
<thead>
<tr>
<th>Time points</th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakavi (N=155)</td>
<td>Placebo (N=153)</td>
<td>Jakavi (N=144)</td>
</tr>
<tr>
<td>Number (%) of subjects with spleen volume reduced by ≥35%</td>
<td>65 (41.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>95% confidence intervals</td>
<td>34.1, 50.1</td>
<td>0, 3.6</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

A significantly higher proportion of patients in the Jakavi group achieved ≥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 ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

<table>
<thead>
<tr>
<th>JAK mutation status</th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakavi</td>
<td>Placebo</td>
<td>Jakavi</td>
</tr>
<tr>
<td>Positive (N=113) n (%)</td>
<td>Negative (N=40) n (%)</td>
<td>Positive (N=121) n (%)</td>
</tr>
<tr>
<td>Number (%) of subjects with spleen volume reduced by ≥35%</td>
<td>54 (47.8)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>Time point</td>
<td>After 24 weeks</td>
<td>After 48 weeks</td>
</tr>
</tbody>
</table>
The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group (p<0.0001 using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo (p<0.0001).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythemia vera and post essential thrombocythemia subgroups.

Polycythemia vera
A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the Jakavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 1). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib treatment at Week 32 or after, limiting the comparison between the two arms after Week 32.
Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT (p=0.0028) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT. (p<0.0001).

**Figure 1** Patients achieving the primary endpoint and components of the primary endpoint at week 32

Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).

**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 MF (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 (Cₘₐₓ) 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 Cₘₐₓ 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 Cₘₐₓ was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.
Distribution
The mean volume of distribution at steady state is approximately 75 litres in MF and PV 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 CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on in vitro studies. In vitro data indicate that ruxolitinib may inhibit P-gp and BCRP.  

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

Linearity/non-linearity
Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations
Effects of age, gender or race
Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in PV patients.

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\textsubscript{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

Blisters
2 years

Bottles
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

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

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

Not all pack sizes or types may be marketed.

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)

EU/1/12/773/002
EU/1/12/773/007-009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.08.2012

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
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 one one side and “L20” debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Polycythaemia vera (PV)
Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

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 in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm$^3$ and 200,000/mm$^3$ and 20 mg twice daily for patients with a platelet count of $>200,000$/mm$^3$. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

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

Dose modifications

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

Dose reductions should be considered if the platelet count decreases below 100,000/mm$^3$, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

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

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

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 for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.
There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm$^3$ and 200,000/mm$^3$. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm$^3$. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

**Hepatic impairment**

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a 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.

**Older people (≥65 years)**

No additional dose adjustments are recommended for older people.

**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$^3$ or absolute neutrophil count less than 500/mm$^3$ (see section 4.2).

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

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see 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. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. 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).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

**Herpes zoster**

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

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

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

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 for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. 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 MF may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of Jakavi contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered, although the utility of the tapering is unproven.

Excipients

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, 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, 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<sub>max</sub> 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<sub>max</sub>. 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<sub>max</sub> 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

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).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

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 safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

Myelofibrosis
In the randomised period of the two pivotal studies, COMFORT-I and COMFORT-II, the median duration of exposure to Jakavi was 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of 301 patients, 111 (36.9%) had a baseline platelet count of between 100,000/mm³ and 200,000/mm³ and 190 (63.1%) had a baseline platelet count of >200,000/mm³.

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

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

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

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3-year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

Polycythaemia vera
The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.
Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%.

The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE)

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Frequency category for MF patients</th>
<th>Frequency category for PV patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CTCAE grade 4 (&lt;6.5g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE grade 3 (&lt;8.0 – 6.5g/dl)</td>
<td>Very common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Any CTCAE grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE grade 4 (&lt;25,000/mm³)</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE grade 3 (50,000 – 25,000/mm³)</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Any CTCAE grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Adverse Drug Reaction (ADR)</td>
<td>Frequency</td>
<td>Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neutropeniab</td>
<td></td>
<td>Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening</td>
</tr>
<tr>
<td>CTCAE grade 4 (~&lt;500/mm³)</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>CTCAE grade 3 (~&lt;1,000 – 500/mm³)</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Any CTCAE grade</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Bruising</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gaina</td>
<td>Very common</td>
<td>Common</td>
</tr>
<tr>
<td>Hypercholesterolaemiab</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>CTCAE grade 1 and 2</td>
<td>-</td>
<td>Very common</td>
</tr>
<tr>
<td>Hypertriglyceridaemiab</td>
<td>-</td>
<td>Very common</td>
</tr>
<tr>
<td>CTCAE grade 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizzinessa</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Headachea</td>
<td>Very common</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulencea</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Constipationa</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised alanine aminotransferaseb</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>CTCAE grade 3 (&gt; 5x – 20 x ULN)</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Any CTCAE grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Raised aspartate aminotransferaseb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CTCAE grade</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensionc</td>
<td>-</td>
<td>Very common</td>
</tr>
</tbody>
</table>

a 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.

b 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.

c Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening
d These ADRs are discussed in the text.
e Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)
Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

Description of selected adverse drug reactions

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

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

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

Thrombocytopenia
In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm$^3$ was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm$^3$ to 200,000/mm$^3$ before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm$^3$ (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

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

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.

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

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

**Infections**

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

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

**Increased systolic blood pressure**

In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 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 MF patients.

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

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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\textsubscript{50} 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 and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

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

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF\textalpha, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

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

Clinical efficacy and safety

Myelofibrosis
Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (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 or high risk 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. The primary efficacy endpoint was proportion of subjects achieving ≥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 ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (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. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

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

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

<table>
<thead>
<tr>
<th></th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jakavi (N=155)</td>
<td>Placebo (N=153)</td>
</tr>
<tr>
<td>Time points</td>
<td>Week 24</td>
<td>Week 48</td>
</tr>
<tr>
<td>Number (%) of subjects with spleen volume reduced by ≥35%</td>
<td>65 (41.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>95% confidence intervals</td>
<td>34.1, 50.1</td>
<td>0, 3.6</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

A significantly higher proportion of patients in the Jakavi group achieved ≥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 ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

<table>
<thead>
<tr>
<th></th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jakavi (N=113)</td>
<td>Placebo (N=40)</td>
</tr>
<tr>
<td></td>
<td>Positive (%)</td>
<td>Negative (%)</td>
</tr>
<tr>
<td>JAK mutation</td>
<td>54 (47.8)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>status</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Number (%) of subjects with spleen volume reduced by ≥35%</td>
<td>36 (32.7)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Time point</td>
<td>After 24 weeks</td>
<td>After 48 weeks</td>
</tr>
</tbody>
</table>

The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.
In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group (p<0.0001 using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo (p<0.0001).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythaemia vera and post essential thrombocythaemia subgroups.

**Polycythaemia vera**

A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the Jakavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 1). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib treatment at Week 32 or after, limiting the comparison between the two arms after Week 32.
Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT (p=0.0028) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT. (p<0.0001).

**Figure 1** Patients achieving the primary endpoint and components of the primary endpoint at week 32

Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).

**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 MF (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 ($C_{\text{max}}$) 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.
Distribution
The mean volume of distribution at steady state is approximately 75 litres in MF and PV 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 CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on in vitro studies. In vitro data indicate that ruxolitinib may inhibit P-gp and BCRP.

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

Linearity/non-linearity
Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations
Effects of age, gender or race
Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in PV patients.

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

Blisters
2 years

Bottles
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

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

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

Not all pack sizes or types may be marketed.

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)

EU/1/12/773/003
EU/1/12/773/010-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.08.2012

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
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

- Periodic Safety Update Reports
The marketing authorisation holder shall submit the first periodic safety update report for this product within 9 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)
The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

An updated RMP shall be submitted annually until renewal.
**Obligation to conduct post-authorisation measures**

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Annually to coincide with the anniversary of European birth date</td>
</tr>
<tr>
<td>Post-Authorisation efficacy study to provide long-term efficacy and safety data of ruxolitinib including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the study B2301.</td>
<td>Week 80 CSR: June 2015&lt;br&gt;Final CSR: December 2019</td>
</tr>
</tbody>
</table>
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
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/1/12/773/001

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

**CARTON OF UNIT PACK CONTAINING BLISTERS**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakavi 5 mg tablets</td>
</tr>
<tr>
<td>Ruxolitinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each tablet contains 5 mg ruxolitinib (as phosphate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains lactose.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
</tr>
<tr>
<td>14 tablets</td>
</tr>
<tr>
<td>56 tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not store above 30°C.</td>
</tr>
</tbody>
</table>
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**

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

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

   EU/1/12/773/004  14 tablets  
   EU/1/12/773/005  56 tablets

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
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK CONTAINING BLISTERS

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.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

Multipack: 168 (3 packs of 56) 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**

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

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

| EU/1/12/773/006 | 168 tablets (3x56) |

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
| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| INTERMEDIATE CARTON OF MULTIPACK CONTAINING BLISTERS |

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.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   **Tablets**

   56 tablets. Component of a multipack. Not to be sold separately.

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**

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

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

EU/1/12/773/006  
168 tablets (3x56)

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
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTERS</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Jakavi 5 mg tablets  
Ruxolitinib

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited

3. **EXPIRY DATE**

EXP

4. **BATCH NUMBER**

Lot

5. **OTHER**

Monday  
Tuesday  
Wednesday  
Thursday  
Friday  
Saturday  
Sunday
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 10 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 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/1/12/773/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLES

Jakavi 10 mg [carton only]
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON OF UNIT PACK CONTAINING BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 10 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets
14 tablets
56 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**

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

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

<table>
<thead>
<tr>
<th>Number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/1/12/773/014</td>
<td>14 tablets</td>
</tr>
<tr>
<td>EU/1/12/773/015</td>
<td>56 tablets</td>
</tr>
</tbody>
</table>

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Jakavi 10 mg
| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| OUTER CARTON OF MULTIPACK CONTAINING BLISTERS |

1. **NAME OF THE MEDICINAL PRODUCT**

   Jakavi 10 mg tablets  
   Ruxolitinib

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

   Each tablet contains 10 mg ruxolitinib (as phosphate).

3. **LIST OF EXCIPIENTS**

   Contains lactose.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Tablets

   Multipack: 168 (3 packs of 56) 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

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/016  168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg
## PARTICULARS TO APPEAR ON THE OUTER PACKAGING

### INTERMEDIATE CARTON OF MULTIPACK CONTAINING BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

   Jakavi 10 mg tablets  
   Ruxolitinib

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

   Each tablet contains 10 mg ruxolitinib (as phosphate).

3. **LIST OF EXCIPIENTS**

   Contains lactose.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   **Tablets**
   56 tablets. Component of a multipack. Not to be sold separately.

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

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/016 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg
## MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

### BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

   Jakavi 10 mg tablets  
   Ruxolitinib

2. **NAME OF THE MARKETING AUTHORITY HOLDING**

   Novartis Europharm Limited

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**

   Monday  
   Tuesday  
   Wednesday  
   Thursday  
   Friday  
   Saturday  
   Sunday
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

**CARTON AND BOTTLE LABEL**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakavi 15 mg tablets</td>
</tr>
<tr>
<td>Ruxolitinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each tablet contains 15 mg ruxolitinib (as phosphate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains lactose (see leaflet for further information).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
</tr>
<tr>
<td>60 tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not store above 30°C.</td>
</tr>
</tbody>
</table>
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/1/12/773/002

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)
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON OF UNIT PACK CONTAINING BLISTERS</td>
</tr>
</tbody>
</table>

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.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Tablets
14 tablets
56 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

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

### 12. MARKETING AUTHORISATION NUMBER(S)

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/1/12/773/007</td>
<td>14 tablets</td>
</tr>
<tr>
<td>EU/1/12/773/008</td>
<td>56 tablets</td>
</tr>
</tbody>
</table>

### 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
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON OF MULTIPACK CONTAINING BLISTERS

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.

4. PHARMACEUTICAL FORM AND CONTENTS
Tablets
Multipack: 168 (3 packs of 56) 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.
<table>
<thead>
<tr>
<th>10.</th>
<th>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
</table>
| 11. | NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER | Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom |
| 12. | MARKETING AUTHORISATION NUMBER(S) | EU/1/12/773/009  
168 tablets (3x56) |
| 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 |
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INTERMEDIATE CARTON OF MULTIPACK CONTAINING BLISTERS

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.

4. PHARMACEUTICAL FORM AND CONTENTS
Tablets
56 tablets. Component of a multipack. Not to be sold separately.

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

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/009  168 tablets (3x56)

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
### MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

#### BLISTERS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakavi 15 mg tablets</td>
</tr>
<tr>
<td>Ruxolitinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis Europharm Limited</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
</tr>
<tr>
<td>Tuesday</td>
</tr>
<tr>
<td>Wednesday</td>
</tr>
<tr>
<td>Thursday</td>
</tr>
<tr>
<td>Friday</td>
</tr>
<tr>
<td>Saturday</td>
</tr>
<tr>
<td>Sunday</td>
</tr>
</tbody>
</table>
### 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.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10.</strong></td>
<td><strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></td>
</tr>
<tr>
<td><strong>11.</strong></td>
<td><strong>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td></td>
<td>[carton only] Novartis Europharm Limited Wimblehurst Road Horsham West Sussex, RH12 5AB United Kingdom</td>
</tr>
<tr>
<td><strong>12.</strong></td>
<td><strong>MARKETING AUTHORISATION NUMBER(S)</strong></td>
</tr>
<tr>
<td></td>
<td>EU/1/12/773/003</td>
</tr>
<tr>
<td><strong>13.</strong></td>
<td><strong>BATCH NUMBER</strong></td>
</tr>
<tr>
<td></td>
<td>Lot</td>
</tr>
<tr>
<td><strong>14.</strong></td>
<td><strong>GENERAL CLASSIFICATION FOR SUPPLY</strong></td>
</tr>
<tr>
<td></td>
<td>Medicinal product subject to medical prescription.</td>
</tr>
<tr>
<td><strong>15.</strong></td>
<td><strong>INSTRUCTIONS ON USE</strong></td>
</tr>
<tr>
<td><strong>16.</strong></td>
<td><strong>INFORMATION IN BRAILLE</strong></td>
</tr>
<tr>
<td></td>
<td>Jakavi 20 mg [carton only]</td>
</tr>
</tbody>
</table>
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON OF UNIT PACK CONTAINING BLISTERS

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td></td>
<td>Jakavi 20 mg tablets Ruxolitinib</td>
</tr>
<tr>
<td>2.</td>
<td>STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td></td>
<td>Each tablet contains 20 mg ruxolitinib (as phosphate).</td>
</tr>
<tr>
<td>3.</td>
<td>LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td></td>
<td>Contains lactose.</td>
</tr>
<tr>
<td>4.</td>
<td>PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td></td>
<td>Tablets</td>
</tr>
<tr>
<td></td>
<td>14 tablets</td>
</tr>
<tr>
<td></td>
<td>56 tablets</td>
</tr>
<tr>
<td>5.</td>
<td>METHOD AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td></td>
<td>Oral use. Read the package leaflet before use.</td>
</tr>
<tr>
<td>6.</td>
<td>SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</td>
</tr>
<tr>
<td></td>
<td>Keep out of the sight and reach of children.</td>
</tr>
<tr>
<td>7.</td>
<td>OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>8.</td>
<td>EXPIRY DATE</td>
</tr>
<tr>
<td></td>
<td>EXP</td>
</tr>
<tr>
<td>9.</td>
<td>SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td></td>
<td>Do not store above 30°C.</td>
</tr>
</tbody>
</table>
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

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

12. MARKETING AUTHORISATION NUMBER(S)

<table>
<thead>
<tr>
<th>Number</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/1/12/773/010</td>
<td>14 tablets</td>
</tr>
<tr>
<td>EU/1/12/773/011</td>
<td>56 tablets</td>
</tr>
</tbody>
</table>

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
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON OF MULTIPACK CONTAINING BLISTERS**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakavi 20 mg tablets</td>
</tr>
<tr>
<td>Ruxolitinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each tablet contains 20 mg ruxolitinib (as phosphate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains lactose.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
</tr>
</tbody>
</table>

Multipack: 168 (3 packs of 56) tablets.

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not store above 30°C.</td>
</tr>
</tbody>
</table>
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 AUTHORITY

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/012  168 tablets (3x56)

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
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INTERMEDIATE CARTON OF MULTIPACK CONTAINING BLISTERS

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.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

56 tablets. Component of a multipack. Not to be sold separately.

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

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/012 168 tablets (3x56)

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
### MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

#### BLISTERS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
<td></td>
</tr>
</tbody>
</table>
|   | Jakavi 20 mg tablets  
|   | Ruxolitinib |
| **2. NAME OF THE MARKETING AUTHORISATION HOLDER** |   |
|   | Novartis Europharm Limited |
| **3. EXPIRY DATE** | EXP |
| **4. BATCH NUMBER** | Lot |
| **5. OTHER** | Monday  
|   | Tuesday  
|   | Wednesday  
|   | Thursday  
|   | Friday  
|   | Saturday  
|   | Sunday |
B. PACKAGE LEAFLET
Package leaflet: Information for the patient

Jakavi 5 mg tablets
Jakavi 10 mg tablets
Jakavi 15 mg tablets
Jakavi 20 mg tablets
ruxolitinib

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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. See section 4.

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.

Jakavi is also used to treat patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

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 in patients with myelofibrosis. Jakavi can help reduce the risk of serious blood or vascular complications.

Polycythaemia vera is a disorder of the bone marrow, in which the marrow produce too many red blood cells. The blood becomes thicker as a result of the increased red blood cells. Jakavi can relieve the symptoms, reduce spleen size and the volume of red blood cells produced in patients with polycythaemia vera by selectively blocking enzymes called Janus Associated Kinases (JAK1 and JAK2), thus potentially reducing 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. It is important that you tell your doctor if you have ever had tuberculosis or if you have been in close contact with someone who has or has had tuberculosis. Your doctor may perform tests to see if you have tuberculosis. It is important that you tell your doctor if you have ever had hepatitis B.
- 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”).
- if you have ever had tuberculosis.
- if you have ever had skin cancer.

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 experience chronic coughing with blood-tinged sputum, fever, night sweats and weight loss (these can be signs of tuberculosis).
- if you have any of the following symptoms or if anyone close to you notices that you have any of these symptoms: confusion or difficulty thinking, loss of balance or difficulty walking, clumsiness, difficulty speaking, decreased strength or weakness on one side of your body, blurred and/or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.
- if you develop painful skin rash with blisters (these are signs of shingles).
- if you notice skin changes. This may require further observation, as certain types of skin cancer (non-melanoma) have been reported.

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 apranevir, 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 in myelofibrosis is 15 mg twice daily or 20 mg twice daily, depending on your blood cell count.
- The recommended starting dose in polycythaemia vera is 10 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 either one single dose or two separate doses of Jakavi only on dialysis days, after the dialysis has been completed. Your doctor will tell you if you should take one or two doses and 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 or fat in the blood (hypertriglyceridaemia)
- abnormal liver function test results
- dizziness
- headache
- urinary tract infections
- weight gain

**Common:**
- frequently passing wind (flatulence)
- constipation
- high blood pressure (hypertension), which may also be the cause of dizziness and headaches

**Uncommon:**
- tuberculosis

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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, bottle label or blister after “EXP”. If your Jakavi tablets are packed in a bottle, they must be used 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 10 mg Jakavi tablet contains 10 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 10 mg tablets are white to almost white round tablets with “NVR” debossed on one side and “L10” 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 supplied in
- blister packs containing 14 or 56 tablets or multipacks containing 168 (3 packs of 56) tablets;
- plastic bottles containing 60 tablets.

Not all packs may be marketed in your country.

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

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Belgie/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

България
Novartis Pharma Services Inc.
Tel.: +359 2 489 98 28

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00
<table>
<thead>
<tr>
<th>Country</th>
<th>Company Name</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danmark</td>
<td>Novartis Healthcare A/S</td>
<td>+45 39 16 84 00</td>
</tr>
<tr>
<td>Deutschland</td>
<td>Novartis Pharma GmbH</td>
<td>+49 911 273 0</td>
</tr>
<tr>
<td>Eesti</td>
<td>Novartis Pharma Services Inc.</td>
<td>+372 66 30 810</td>
</tr>
<tr>
<td>Ελλάδα</td>
<td>Novartis (Hellas) A.E.B.E.</td>
<td>+30 210 281 17 12</td>
</tr>
<tr>
<td>España</td>
<td>Novartis Farmacéutica, S.A.</td>
<td>+34 93 306 42 00</td>
</tr>
<tr>
<td>France</td>
<td>Novartis Pharma S.A.S.</td>
<td>+33 1 55 47 66 00</td>
</tr>
<tr>
<td>Hrvatska</td>
<td>Novartis Hrvatska d.o.o.</td>
<td>+385 1 6274 220</td>
</tr>
<tr>
<td>Ireland</td>
<td>Novartis Ireland Limited</td>
<td>+353 1 260 12 55</td>
</tr>
<tr>
<td>Ísland</td>
<td>Vistor hf.</td>
<td>+354 535 7000</td>
</tr>
<tr>
<td>Italia</td>
<td>Novartis Farma S.p.A.</td>
<td>+39 02 96 54 1</td>
</tr>
<tr>
<td>Κύπρος</td>
<td>Novartis Pharma Services Inc.</td>
<td>+357 22 690 690</td>
</tr>
<tr>
<td>Lettija</td>
<td>Novartis Pharma Services Inc.</td>
<td>+371 67 887 070</td>
</tr>
<tr>
<td>Malta</td>
<td>Novartis Pharma Services Inc.</td>
<td>+356 2122 2872</td>
</tr>
<tr>
<td>Nederland</td>
<td>Novartis Pharma B.V.</td>
<td>+31 26 37 82 111</td>
</tr>
<tr>
<td>Norge</td>
<td>Novartis Norge AS</td>
<td>+47 23 05 20 00</td>
</tr>
<tr>
<td>Österreich</td>
<td>Novartis Pharma GmbH</td>
<td>+43 1 86 6570</td>
</tr>
<tr>
<td>Polska</td>
<td>Novartis Poland Sp. z o.o.</td>
<td>+48 22 375 4888</td>
</tr>
<tr>
<td>Portugal</td>
<td>Novartis Farma - Produtos Farmacêuticos, S.A.</td>
<td>+351 21 000 8600</td>
</tr>
<tr>
<td>România</td>
<td>Novartis Pharma Services Romania SRL</td>
<td>+40 21 31299 01</td>
</tr>
<tr>
<td>Slovenija</td>
<td>Novartis Pharma Services Inc.</td>
<td>+386 1 300 75 50</td>
</tr>
<tr>
<td>Slovenská republika</td>
<td>Novartis Slovakia s.r.o.</td>
<td>+421 2 5542 5439</td>
</tr>
<tr>
<td>Suomi/Finland</td>
<td>Novartis Finland Oy</td>
<td>+358 (0)10 6133 200</td>
</tr>
<tr>
<td>Sverige</td>
<td>Novartis Sverige AB</td>
<td>+46 8 732 32 00</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Novartis Pharmaceuticals UK Ltd.</td>
<td>+44 1276 698370</td>
</tr>
</tbody>
</table>

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