ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jakavi 5 mg tablets
Each tablet contains 5 mg ruxolitinib (as phosphate).

Excipient with known effect
Each tablet contains 71.45 mg lactose monohydrate.

Jakavi 10 mg tablets
Each tablet contains 10 mg ruxolitinib (as phosphate).

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

Jakavi 15 mg tablets
Each tablet contains 15 mg ruxolitinib (as phosphate).

Excipient with known effect
Each tablet contains 214.35 mg lactose monohydrate.

Jakavi 20 mg tablets
Each tablet contains 20 mg ruxolitinib (as phosphate).

Excipient with known effect
Each tablet contains 285.80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Jakavi 5 mg tablets
Round curved white to almost white tablets of approximately 7.5 mm in diameter with “NVR” debossed on one side and “L5” debossed on the other side.

Jakavi 10 mg tablets
Round curved white to almost white tablets of approximately 9.3 mm in diameter with “NVR” debossed on one side and “L10” debossed on the other side.

Jakavi 15 mg tablets
Ovaloid curved white to almost white tablets of approximately 15.0 x 7.0 mm with “NVR” debossed on one side and “L15” debossed on the other side.

Jakavi 20 mg tablets
Elongated curved white to almost white tablets of approximately 16.5 x 7.4 mm with “NVR” debossed 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 medicinal products.

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 (MF) is based on platelet counts (see Table 1):

Table 1 Starting doses in myelofibrosis

Platelet count	**Starting dose**
Greater than 200,000/mm^3	20 mg orally twice daily
100,000 to 200,000/mm^3	15 mg orally twice daily
75,000 to less than 100,000/mm^3	10 mg orally twice daily
50,000 to less than 75,000/mm^3	5 mg orally twice daily

The recommended starting dose of Jakavi in polycythaemia vera (PV) is 10 mg given orally twice daily.

Dose modifications
Doses may be titrated based on efficacy and safety.

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

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

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

Dose reductions should be considered if the platelet count decreases during treatment as outlined in Table 2, with the goal of avoiding dose interruptions for thrombocytopenia.

Table 2 Dosing recommendation for thrombocytopenia

	Dose at time of platelet decline				
	25 mg twice daily	20 mg twice daily	15 mg twice daily	10 mg twice daily	5 mg twice daily
Platelet count	**New dose**				
100,000 to <125,000/mm^3	20 mg twice daily	15 mg twice daily	No change	No change	No change
75,000 to <100,000/mm^3	10 mg twice daily	10 mg twice daily	10 mg twice daily	No change	No change
50,000 to <75,000/mm^3	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No change
Less than 50,000/mm^3	Hold	Hold	Hold	Hold	Hold

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

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

More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of ruxolitinib-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 ruxolitinib 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 ruxolitinib 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 ruxolitinib and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Ruxolitinib dose can be titrated to reduce the risk of cytopenia.

Elderly patients (≥65 years)
No additional dose adjustments are recommended for elderly patients.

Paediatric population
The safety and efficacy of Jakavi in children and adolescents 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 absoute 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

Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with Jakavi. Patients should be assessed for the risk of developing serious infections. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly. Treatment with Jakavi should not be started until active serious infections have resolved.

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

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

Lipid abnormalities/elevations

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

Special populations

Renal impairment
The starting dose of Jakavi should be reduced in patients with severe renal impairment. 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 with Jakavi was associated with manageable cytopenias (see section 4.2 for dose modifications during cytopenias).

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 experienced severe adverse 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, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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

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

Dual CYP2C9 and CYP3A4 inhibitors
In healthy subjects co-administration of ruxolitinib (10 mg single dose) with a dual CYP2C9 and CYP3A4 inhibitor, fluconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 47% and 232%, respectively, than with ruxolitinib alone.

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

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

Other interactions to be considered affecting ruxolitinib

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)
In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

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

Effects of ruxolitinib on other medicinal products

Substances transported by P-glycoprotein or other transporters
Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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 childbearing potential/Contraception

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

Myelofibrosis
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 (83.8%), thrombocytopenia (80.5%) and neutropenia (20.8%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (33.3%), other bleeding (including epistaxis, post-procedural haemorrhage and haematuria) (24.3%) and dizziness (21.9%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (40.7%), raised aspartate aminotransferase (31.5%) and hypertriglyceridaemia (25.2%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypertriglyceridaemia or raised aspartate aminotransferase, nor CTCAE grade 4 raised alanine aminotransferase or hypercholesterolaemia were observed.

Discontinuation due to adverse events, regardless of causality, was observed in 30.0% of patients.

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

The three most frequent non-haematological adverse reactions were weight gain (20.3%), dizziness (19.4%) and headache (17.9%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as adverse reactions were raised alanine aminotransferase (45.3%), raised aspartate aminotransferase (42.6%), and hypercholesterolaemia (34.7%). No CTCAE grade 4 raised alanine aminotransferase or hypercholesterolaemia, and one CTCAE grade 4 raised aspartate aminotransferase were observed.

Discontinuation due to adverse events, regardless of causality, was observed in 19.4% of patients.

Tabulated list of adverse drug reactions from clinical studies

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

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

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 3) 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); not known (cannot be estimated from the available data).

Table 3 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE, RESPONSE 2)

Adverse drug reaction	**Frequency category for MF patients**	**Frequency category for PV patients**
Infections and infestations		
Urinary tract infections[a,e]	Very common	Very common
Herpes zoster[a,e]	Very common	Very common
Pneumonia	Very common	Common
Sepsis	Common	Uncommon
Tuberculosis	Uncommon	Not known[f]
HBV reactivation	Not known[f]	Uncommon
Blood and lymphatic system disorders[b,e]		
Anaemia[b]		
CTCAE[d] grade 4 (<6.5g/dl)	Very common	Uncommon
CTCAE[d] grade 3 (<8.0 – 6.5g/dl)	Very common	Common
Any CTCAE[d] grade	Very common	Very common
Thrombocytopenia[b]		
CTCAE[d] grade 4 (<25,000/mm^3)	Common	Uncommon

CTCAE[d] grade 3 (50,000 – 25,000/mm^3)	Very common	Common
Any CTCAE[d] grade	Very common	Very common
Neutropenia[b]		
CTCAE[d] grade 4 (<500/mm^3)	Common	Uncommon
CTCAE[d] grade 3 (<1,000 – 500/mm^3)	Common	Uncommon
Any CTCAE[d] grade	Very common	Common
Pancytopenia[b, c]	Common	Common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Bruising	Very common	Very common
Gastrointestinal bleeding	Very common	Common
Intracranial bleeding	Common	Uncommon
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Very common	Very common
Metabolism and nutrition disorders		
Hypercholesterolaemia[b] any CTCAE[d] grade	Very common	Very common
Hypertriglyceridaemia[b] any CTCAE[d] grade	Very common	Very common
Weight gain[a]	Very common	Very common
Nervous system disorders		
Dizziness[a]	Very common	Very common
Headache[a]	Very common	Very common
Gastrointestinal disorders		
Elevated lipase, any CTCAE[d] grade	Very common	Very common
Constipation[a]	Very common	Very common
Flatulence[a]	Common	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[b]		
CTCAE[d] grade 3 (> 5x – 20 x ULN)	Common	Common
Any CTCAE[d] grade	Very common	Very common
Raised aspartate aminotransferase[b]		
Any CTCAE[d] grade	Very common	Very common

Vascular disorders		
Hypertension[a]	Very common	Very common

[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] Pancytopenia is defined as haemoglobin level <100 g/l, platelet count $<100x10^9$/l, and neutrophil count $<1.5x10^9$/l (or low white blood cell count of grade 2 if neutrophil count is missing), simultaneously in the same lab assessment

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

[e] These ADRs are discussed in the text.

[f] ADR derived from post-marketing experience

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

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

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (40.8% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 2.7%, 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 ruxolitinib and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving ruxolitinib and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm^3 to 200,000/mm^3 before starting ruxolitinib had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 38.5%).

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

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 phase 3 studies in PV patients, neutropenia was reported in 1.6% of patients exposed to ruxolitinib compared to 7% in reference treatments. In the ruxolitinib arm one patient developed CTCAE grade 4 neutropenia. An extended follow-up of patients treated with ruxolitinib showed 2 patients reporting 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 ruxolitinib 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 ruxolitinib 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 ruxolitinib compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to ruxolitinib and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to ruxolitinib compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with ruxolitinib and 10.3% treated with reference treatments.

During the long-term follow-up of phase 3 clinical studies in MF, the cumulative frequency of bleeding events increased proportionally to the increase in the follow-up time. Bruising events were the most frequently reported bleeding events (33.3%). Intracranial and gastrointestinal bleeding events were reported in 1.3% and 10.1% of patients respectively.

In the comparative period of phase 3 studies in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 16.8% of patients treated with ruxolitinib, 15.3% of patients receiving best available therapy in RESPONSE study and 12.0% of patients receiving best available therapy in RESPONSE 2 study. Bruising was reported in 10.3% of patients treated with ruxolitinib, 8.1% of patients receiving best available therapy in RESPONSE study and 2.7% of patients receiving best available therapy in RESPONSE 2 study. No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving ruxolitinib. One patient treated with ruxolitinib experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage, gingival bleeding) were reported in 8.7% of patients treated with ruxolitinib, 6.3% of patients treated with best available therapy in RESPONSE study and 6.7% of patients treated with best available therapy in RESPONSE 2 study.

During the long-term follow-up of phase 3 studies in PV, the cumulative frequency of bleeding events increased proportionally to the increase in the follow-up time. Bruising events were the most frequently reported bleeding events (17.4%). Intracranial and gastrointestinal bleeding events were reported in 0.3% and 3.5% of patients respectively.

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 phase 3 studies in PV patients, one (0.5%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was similar in PV (4.3%) patients and MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients. Pneumonia was reported in 0.5% of patients treated with ruxolitinib compared to 1.6% of patients in reference treatments. No patients in the ruxolitinib arm reported sepsis or tuberculosis.

During long-term follow-up of phase 3 studies in PV, frequently reported infections were urinary tract infections (11.8%), herpes zoster (14.7%) and pneumonia (7.1%). Sepsis was reported in 0.6% of patients. No patients reported tuberculosis in long-term follow-up.

Elevated lipase
In the randomised period of the RESPONSE study, the worsening of lipase values was higher in the ruxolitinib arm compared to the control arm, mainly due to the differences among grade 1 elevations (18.2% vs 8.1%). Grade ≥2 elevations were similar between treatment arms. In RESPONSE 2, the frequencies were comparable between the ruxolitinib and the control arm (10.8% vs 8%). During long-term follow-up of phase 3 PV studies, 7.4% and 0.9% of patients reported grade 3 and grade 4 elevation of lipase values. No concurrent signs and symptoms of pancreatitis with elevated lipase values were reported in these patients.

In phase 3 studies in MF, high lipase values were reported in 18.7% and 19.3% of patients in the ruxolitinib arms compared to 16.6% and 14.0% in the control arms in COMFORT-I and COMFORT-II studies, respectively. In patients with elevated lipase values, no concurrent signs and symptoms of pancreatitis were reported.

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 ruxolitinib 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 ruxolitinib 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: L01EJ01

Mechanism of action

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

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

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

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 MF, post-polycythaemia vera MF or post-essential thrombocythaemia MF). 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. Patients with platelet counts ≤100,000/mm^3 were not eligible for enrolment in COMFORT studies but 69 patients were enrolled in the EXPAND study, a Phase Ib, open label, dose-finding study in patients with MF (primary MF, post-polycythaemia vera MF or post-essential thrombocythaemia MF) and baseline platelet counts ≥50,000 and <100,000/mm^3.

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 MF 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 ruxolitinib 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 4 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)

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

A significantly higher proportion of patients in the Jakavi group achieved ≥35% reduction from baseline in spleen volume (Table 4) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary MF, post-polycythaemia vera MF, post-essential thrombocythaemia MF).

Table 5 Percentage of patients with ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

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

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-I, after a median follow–up of 61.7 months, the death rate in patients randomised to the ruxolitinib arm was 44.5% (69 of 155 patients) versus 53.2% (82 of 154) in patients randomised to placebo. There was a 31% reduction in the risk of death in the ruxolitinib arm as compared to placebo (HR 0.69; 95% CI 0.50-0.96; p=0.025).

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.

In COMFORT-II, after a median follow-up of 55.9 months, the death rate in patients randomised to the ruxolitinib arm was 40.4% (59 of 146 patients) versus 47.9% (35 of 73 patients) in patients randomized to best available therapy (BAT). There was a 33% reduction in risk of death in the ruxolitinib arm compared to the BAT arm (HR 0.67; 95% CI 0.44-1.02; p=0.062).

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%).

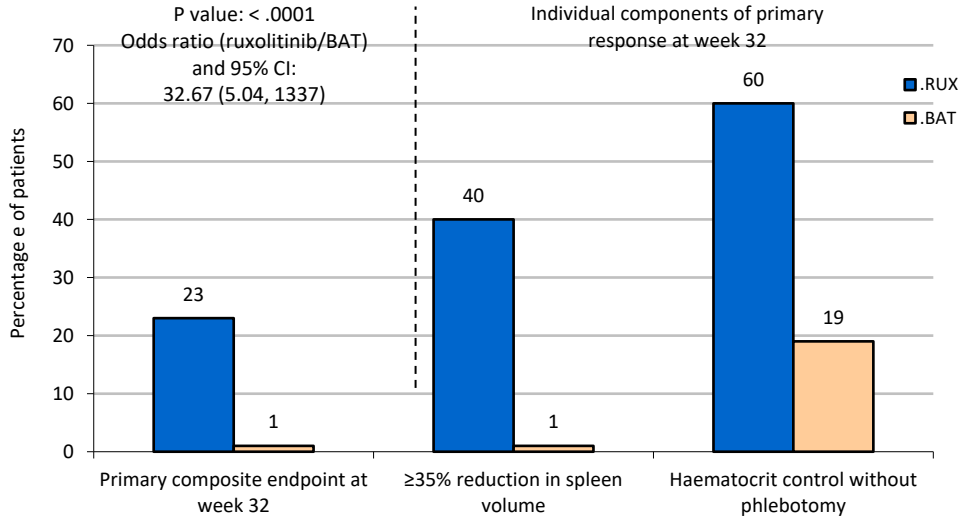
Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. 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 (23%) 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 18.8% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 40% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 1).

Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.0% on BAT (p=0.0013) and the proportion of patients achieving a durable primary response at week 48 was 20% on Jakavi and 0.9% on BAT (p<0.0001).

Figure 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%).

Additional analyses from the RESPONSE study to assess durability of response were conducted at week 80 and week 256 following randomisation. Out of 25 patients who had achieved primary response at week 32, 3 patients had progressed by week 80 and 6 patients by week 256. The probability to have maintained a response from week 32 up to week 80 and week 256 was 92% and 74%, respectively (see Table 6).

Table 6 Durability of primary response in the RESPONSE study

	Week 32	Week 80	Week 256
Primary response achieved at week 32* n/N (%)	25/110 (23%)	n/a	n/a
Patients maintaining primary response	n/a	22/25	19/25
Probability of maintaining primary response	n/a	92%	74%
* According to the primary response composite endpoint criteria: absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline. n/a: not applicable			

A second randomised, open label, active-controlled phase 3b study (RESPONSE 2) was conducted in 149 PV patients who were resistant to, or intolerant of, hydroxyurea but without palpable splenomegaly. The primary endpoint defined as the proportion of patients achieving HCT control (absence of phlebotomy eligibility) at week 28 was met (62.2% in the Jakavi arm versus 18.7% in the BAT arm). The key secondary endpoint defined as the proportion of patients achieving complete haematological remission at week 28 was also met (23.0% in the Jakavi arm versus 5.3% in the BAT arm).

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 and PV (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 [^{14}C]-labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74% of radioactivity excreted in urine and 22% via faeces. Unchanged parent substance accounted for less than 1% of the excreted total radioactivity.

Linearity/non-linearity

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

Special populations

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

In juvenile rat studies, administration of ruxolitinib resulted in effects on growth and bone measures. Reduced bone growth was observed at doses ≥5 mg/kg/day when treatment started on postnatal day 7 (comparable to human newborn) and at ≥15 mg/kg/day when treatment started on postnatal days 14 or 21 (comparable to human infant, 1–3 years). Fractures and early termination of rats were observed at doses ≥30 mg/kg/day when treatment was started on postnatal day 7. Based on unbound AUC, the exposure at the NOAEL (no observed adverse effect level) in juvenile rats treated as early as postnatal day 7 was 0.3-fold that of adult patients at 25 mg twice daily, while reduced bone growth and fractures occurred at exposures that were 1.5- and 13-fold that of adult patients at 25 mg twice daily, respectively. The effects were generally more severe when administration was initiated earlier in the postnatal period. Other than bone development, the effects of ruxolitinib in juvenile rats were similar to those in adult rats. Juvenile rats are more sensitive than adult rats to ruxolitinib toxicity.

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 K30
Hydroxypropylcellulose 300 to 600 cps
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

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.

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Jakavi 5 mg tablets
EU/1/12/773/004-006

Jakavi 10 mg tablets
EU/1/12/773/014-016

Jakavi 15 mg tablets
EU/1/12/773/007-009

Jakavi 20 mg tablets
EU/1/12/773/010-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2012
Date of latest renewal: 24 April 2017

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 Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

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

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTERS

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

CARTON OF UNIT PACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/014	14 tablets
EU/1/12/773/015	56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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 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

CARTON OF UNIT PACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/007 14 tablets
EU/1/12/773/008 56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

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.

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 15 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

CARTON OF UNIT PACK

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

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/010	14 tablets
EU/1/12/773/011	56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

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

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

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
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

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

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

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 or any other infections. 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.

<u>Blood tests</u>
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. Your doctor will carefully check if you have any signs or symptoms of infection before starting and during your treatment with Jakavi. Your doctor will also regularly check the level of lipids (fat) in your blood.

<u>Stopping Jakavi</u>
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
This medicine is not intended for use by children or adolescents aged below 18 years because it has not been studied in this age group.

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 amprenavir, 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 and sodium
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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 5 mg twice daily, 10 mg twice daily, 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.
- 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 (very 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*)) (very 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 (may affect more than 1 in 10 people):
- high level of cholesterol or fat in the blood (*hypertriglyceridaemia*)
- abnormal liver function test results
- dizziness
- headache
- urinary tract infections
- weight gain
- fever, cough, difficult or painful breathing, wheezing, pain in chest when breathing (possible symptoms of pneumonia)
- high blood pressure (*hypertension*), which may also be the cause of dizziness and headaches
- constipation
- high level of lipase in the blood

Common (may affect up to 1 in 10 people):
- reduced number of all three types of blood cells - red blood cells, white blood cells, and platelets (*pancytopenia*)
- frequently passing wind (*flatulence*)

Uncommon (may affect up to 1 in 100 people):
- tuberculosis
- recurrence of hepatitis B infection (which can cause yellowing of the skin and eyes, dark brown-colored urine, right-sided stomach pain, fever and feeling nauseous or being sick).

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 or blister after “EXP”.

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

Not all packs may be marketed in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

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

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

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

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

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

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

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom (Northern Ireland)
Novartis Ireland Limited
Tel: +44 1276 698370

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