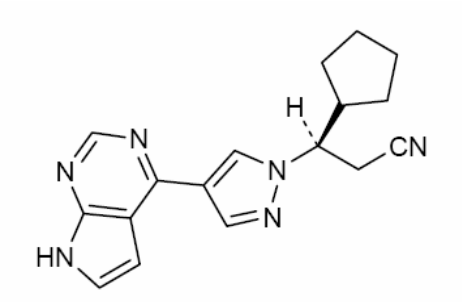
JAKAVI®

Ruxolitinib

NAME OF THE MEDICINE

Structural formula:



The active ingredient of Jakavi is ruxolitinib (as the phosphate salt) or (*R*)-3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate

INN: ruxolitinib

CAS name .: 1H-Pyrazole-1-propanenitrile, β-cyclopentyl-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-, (βR)-, phosphate (1:1); 941678-49-5

CAS Number.: 1092939-17-7

Molecular formula: $C_{17}H_{18}N_6$

Molecular weight of the phosphate salt: 404.36

Molecular weight of the free base: 306.37

DESCRIPTION

Ruxolitinib phosphate is a white to almost white powder. It is highly soluble in water, most soluble at low pH (pH 3.3) at 37°C. The pKa is 4.3 and 11.8. The BCS is Class 1.

Jakavi tablets contain 5 mg, 15 mg and 20 mg of ruxolitinib as the phosphate salt.

Excipients

Jakavi tablets contain the following excipients: cellulose, microcrystalline; magnesium stearate; silica, colloidal anhydrous; sodium starch glycollate type A; hydroxypropylcellulose; povidone; lactose.

PHARMACOLOGY

Mechanism of action (MOA)

Ruxolitinib is an inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 with nanomolar potency. JAKs mediate the signaling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. JAK signalling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAKSTAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells.

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) 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.

Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies. In an acute mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, decreased circulating inflammatory cytokines (e.g.: TNF-α, IL-6) and resulted in significantly prolonged survival.

Pharmacodynamics

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

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFalpha, IL-6, and CRP in subjects with MF were decreased following treatment with ruxolitinib. Patients with myelofibrosis did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

Pharmacokinetics

Absorption:

Ruxolitinib is a Class 1 molecule under the Biopharmaceutical Classification System, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies,

ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (Cmax) achieved approximately 1 hour post-dose. Based on a mass balance study in humans, oral absorption of ruxolitinib was 95% or greater. Mean ruxolitinib Cmax and total exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean Cmax was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) upon dosing with a high-fat meal.

Distribution:

The apparent volume of distribution at steady-state is 53-65 L in myelofibrosis patients. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins in vitro is approximately 97%, mostly to albumin.

Metabolism:

In vitro studies indicate that CYP3A4 is the major enzyme responsible for metabolism of ruxolitinib. Parent compound is the predominant entity in humans representing approximately 60% of the drug-related material in circulation. Two major and active metabolites were identified in plasma of healthy subjects representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contribute to 18% of the overall pharmacodynamics of ruxolitinib.

Elimination:

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

Pharmacokinetics in special patient groups

Effects of age, gender, or race

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

Paediatric

The safety and effectiveness of Jakavi in paediatric patients have not been established.

Renal insufficiency

Following a single ruxolitinib dose of 25 mg, the pharmacokinetics were 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 most markedly in the subjects with end stage renal disease requiring hemodialysis. Ruxolitinib is not removed by dialysis. A dose modification is recommended for patients with moderate to severe renal impairment (Clcr less than 60 mL/min). For patients with end stage renal disease a modification of the dosing schedule is recommended. Jakavi should be avoided in patients with end stage renal disease (Clcr less than 15 mL/min) not undergoing dialysis and in patients with moderate to severe renal impairment with platelet counts less than 100 $x10^9$/L (see Dosage and Administration section).

Hepatic insufficiency

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the pharmacokinetics and pharmacodynamics of ruxolitinib were assessed. The mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal hepatic function and indicating no clear relationship to the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). A dose reduction is recommended for patients with hepatic impairment (see Dosage and Administration section).

CLINICAL TRIALS

Two randomized Phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with Myelofibrosis (Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis or Post-Essential Thrombocythemia-Myelofibrosis) In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate 2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group Consensus Criteria (IWG). The prognostic factors that comprise the IWG criteria consist of age >65 years, presence of constitutional symptoms (weight loss, fever, night sweats) anaemia (haemoglobin <10 g/dL), leukocytosis (history of WBC >25 X 10^9/L) and circulating blasts ≥1%. The starting dose of Jakavi was based on platelet count. A baseline platelet count > 100 x 10^9/L was required for trial entry. Patients with a platelet count between 100 and 200X 10^9/L were started on Jakavi 15 mg twice daily and patients with a platelet count >200X 10^9/L were started on Jakavi 20 mg twice daily. Doses were then individualized based upon tolerability and efficacy with maximum doses of 20 mg twice daily for patients with platelet counts between 100 to ≤125X 10^9/L, of 10 mg twice daily for patients with platelet counts between 75 to ≤100X 10^9/L, and of 5 mg twice daily for patients with platelet counts between 50 to ≤75X 10^9/L.

COMFORT-I was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. Patients were dosed with Jakavi or matching placebo. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at Week 24 as measured by MRI or 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 from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, change in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary and overall survival.

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

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

In COMFORT-I, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 68 years with 61% of patients older than 65 years and 54% male. Fifty percent (50%) of patients had primary myelofibrosis, 31% had post-polycythemia myelofibrosis and 18% had post-essential thrombocythemia myelofibrosis. Twenty-one (21%) of patients had red blood transfusions within 8 weeks of enrolment in the study. The median platelet count was 251X 10^9/L. Seventy-six percent of patients had the mutation encoding the V617F substitution present in the JAK protein. Patients had a median palpable spleen length of 16 cm. At baseline 37.4% of the patients in the Jakavi arm had grade 1 anaemia , 31.6% grade 2 and 4.5% grade 3, while in the placebo arm 35.8% had grade 1, 35.1% grade 2, 4.6% grade 3, and 0.7% grade 4 . Grade 1 thrombocytopenia was found in 12.9 % of patients in the Jakavi arm and 13.2% in the placebo arm.

In COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 66 years with 52% of patients older than 65 years and 57% male. Fifty-three percent (53%) of the subjects had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis, and 16% had post-essential thrombocythemia myelofibrosis. 19% of patients were considered transfusion dependent at baseline. Patients had a median palpable spleen length of 15 cm.

At baseline 34.2% of the patients in the Jakavi arm had grade 1 anaemia , 28.8% grade 2, and 7.5% grade 3, while in the BAT arm 37% had grade 1, 27.4% grade 2, 13.7% grade 3, and 1.4% grade 4 . Thrombocytopenia of grade 1 was found in 8.2% of patients in the Jakavi arm, and 9.6% in the BAT arm.

Efficacy analyses of the primary endpoint in COMFORT-I and COMFORT-II are presented in Table 1 below. A significantly larger proportion of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline in both studies compared to placebo in COMFORT-I and best available therapy in COMFORT-II.

Table 1 Percent of Patients with ≥35% Reduction from Baseline in Spleen Volume at Week 24 in COMFORT-I and at Week 48 in COMFORT-II (ITT)

	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
% difference between treatments (95% CI[a])	41.3 (32.8, 48.7)		28.5 (19.6, 35.2)	
P-value	< 0.0001		< 0.0001	

a: by Agresti-Caffo method (Agresti and Caffo; The American Statistician, 2000)

In COMFORT-I, 41.9% of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline compared with 0.7% in the placebo group at Week 24. A similar proportion of patients in the Jakavi group achieved a ≥50% reduction in the exploratory efficacy endpoint of palpable spleen length.

In COMFORT-II, 28.5% of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline compared with none (0%) in the best available therapy group at Week 48. A secondary endpoint was the proportion of patients achieving a ≥35% reduction of spleen volume at Week 24. A significantly larger proportion of patients in the Jakavi group 46 (31.9%) achieved a ≥35% reduction in spleen volume from baseline compared to no (0%) patients in the best available therapy group (p-value <0.0001).

A exploratory subgroup analysis showed a significantly higher proportion of patients in the Jakavi group achieved ≥ 35% reduction from baseline in spleen volume regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis).

Figure 1 shows a waterfall plot of the percent change from baseline in spleen volume at Week 24 in COMFORT-I. Among the 139 patients in the Jakavi group who had both baseline spleen volume at Week 24, with a median reduction of 33%. Among the 106 patients in the placebo group who had both baseline and Week 24 spleen volume evaluations, there was a median increase of 8.5%.

Figure 1 Waterfall Plot of Percent Change From Baseline in Spleen Volume at Week 24 (Observed Cases) COMFORT- I

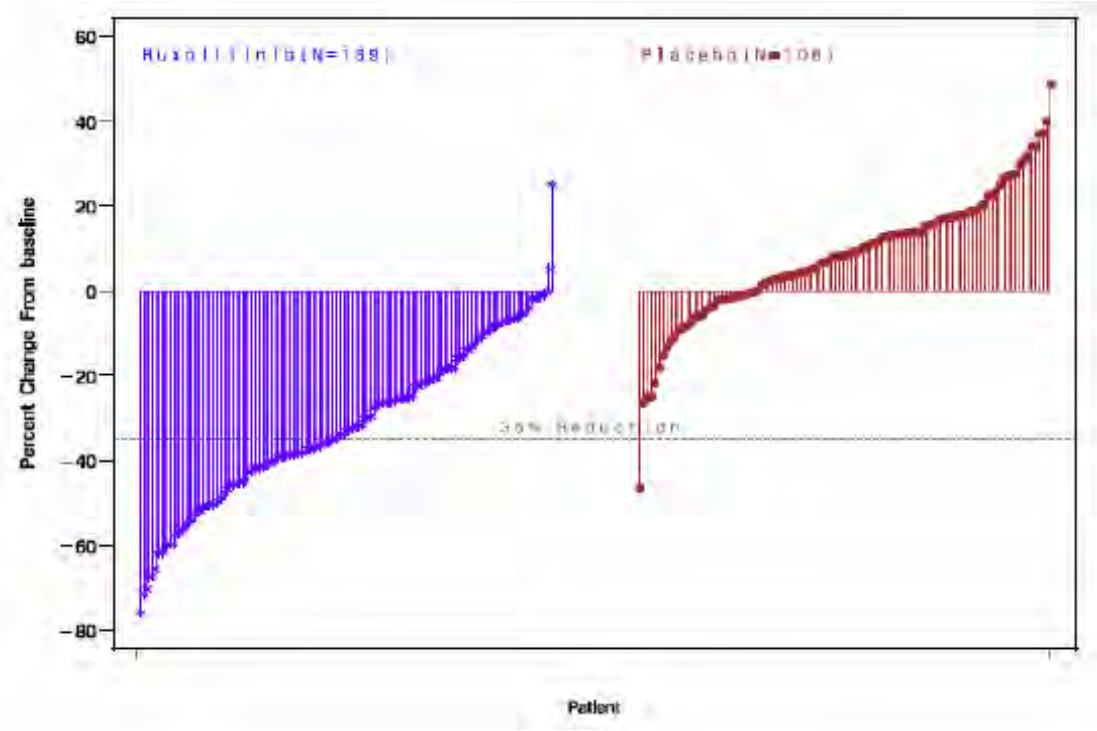
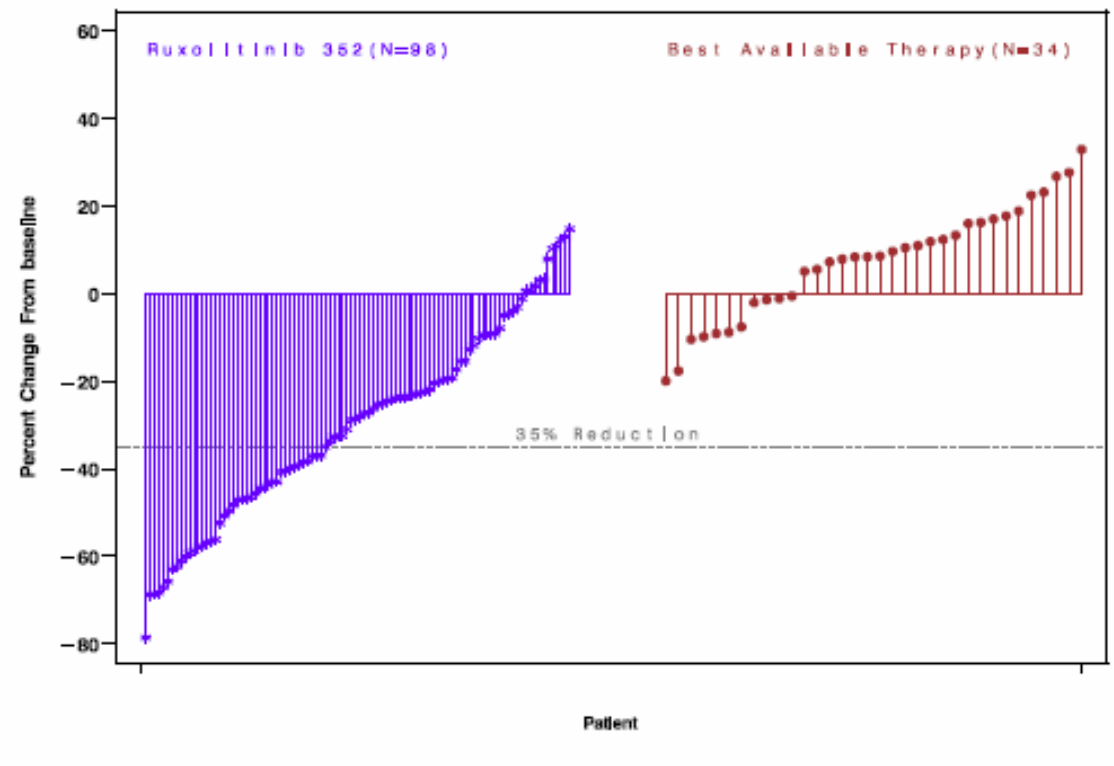


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the Jakavi group who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was 28%. Among the 34 patients in the Best Available Therapy group who had both baseline and Week 48 spleen volume evaluations, there was a median increase of 8.5%.

Figure 2 Waterfall Plot of Percent Change from Baseline in Spleen Volume at Week 48 in COMFORT-II



The probability of duration from 1st ≥35% reduction of spleen volume to 25% increase from nadir and loss of response in COMFORT-I and COMFORT-II is shown in Table 2 below .

Table 2 Kaplan-Meier Analysis of Duration from 1st ≥ 35% Reduction of Spleen Volume to 25% Increase from Nadir and Loss of Response in Jakavi Patients (COMFORT- I and - II)

Statistics	Jakavi (COMFORT-I)	Jakavi (COMFORT-II)
Probability of >12 weeks of duration (95% CI)	0.98 (0.89, 1.00)	0.92 (0.82, 0.97)
Probability of >24 weeks of duration (95% CI)	0.89 (0.75, 0.95)	0.87 (0.76, 0.93)
Probability of >36 weeks of duration (95% CI)	0.71 (0.41, 0.88)	0.77 (0.63, 0.87)
Probability of >48 weeks of duration (95% CI)	not applicable	0.52 (0.18, 0.78)

Among the 80 patients that showed a ≥35% reduction at any time point in COMFORT-I and of the 69 patients in COMFORT-II, the probability that a patient would maintain a response on Jakavi for at least 24 weeks was 89% and 87% in COMFORT-I and COMFORT-II

respectively and the probability of maintaining a response for at least 48 weeks was 52% in COMFORT -II.

Overall survival (OS) was a secondary endpoint on both COMFORT studies. Median OS times had not been reached for either treatment arm in both studies. OS data from COMFORT-I demonstrate a risk of death reduced with Jakavi treatment by 50% (median follow-up: 51 weeks, HR:0.499, 95% CI, 0.254, 0.980; p=0.04), 13 out of 155 patients (8.4%) died in the Jakavi group and 24 out of 154 patients (15.6%) died in the placebo group with OS time censored for 142 (91.6%) and 130 (84.4%) in ruxolitinib and placebo arms, respectively. With 61.1 weeks of follow up COMFORT II OS did not demonstrate a difference between the Jakavi and BAT arm (median follow-up:61.1 weeks; HR:1.01, 95% CI, 0.32, 3.24; p=0.95) with 11 (7.5%) deaths in the ruxolitinib and 4 (5.5%) in the placebo arm, OS time was censored for 135 (92.5%) and 69 (94.5%) patients in ruxolitinib and BAT arms,respectively.

In COMFORT-I, a median follow-up analysis of 102 weeks showed that 27 out of 155 patients randomized to ruxolitinib and 41 out of 154 patients randomized to placebo died. This representing an overall survival (OS) benefit in favor of ruxolitinib (HR=0.58; 95% CI, 0.36-0.95).

In COMFORT-II, a median follow-up analysis of 112 weeks showed that 14% (20 out of 146 patients randomized to ruxolitinib) and 22% (16 out of 73 patients randomized to best available therapy) died. Patients randomized to ruxolitinib showed longer OS than those randomized to BAT (HR = 0.51; 95% CI, 0.27-0.99).

The impact of Jakavi on myelofibrosis-associated symptoms was assessed in COMFORT-I only. In COMFORT-I symptoms of MF (night sweats, itchiness, abdominal discomfort, pain under the ribs, early satiety, bone or muscle pain) were captured using the modified MFSAF diary v2.0 as an electronic diary, which subjects completed daily. The change from Baseline in the Week 24 total score was a secondary endpoint in this study. A significantly larger proportion of subjects in the Jakavi group achieved a ≥50% improvement from Baseline in the Week 24 total symptom score compared with the placebo group (45.9% and 5.3%, respectively, p <0.0001 using the Chi-Squared test).

An improvement in overall quality of life was measured by the exploratory efficacy endpoint, EORTC QLQ-C30, in both COMFORT-I and COMFORT-II. COMFORT-I compared Jakavi to placebo at 24 weeks and COMFORT-II compared Jakavi to best available therapy at 48 weeks. At baseline for both studies, EORTC QLQ-C30 individual subscale scores for the Jakavi and comparator groups were similar. At Week 24 in COMFORT-I, the Jakavi group showed significant improvement in the global health status/quality of life of the EORTC QLQ-C30 compared with the placebo group (mean change of +12.3 and -3.4 for Jakavi and

placebo, respectively, p <0.0001). At week 24 and week 48, the Jakavi group in COMFORT-II showed a trend towards greater improvement of global health status/quality of life compared to best available therapy (week 24: 8.4 (Jakavi) vs 5.2 (BAT); week 48: 9.1 (Jakavi) vs 3.4 (BAT), an exploratory endpoint, consistent with the COMFORT-I findings.

Recent clinical trial data from two ongoing trials (EXPAND and Study 258) support the use of ruxolitinib at lower starting dose of ≤ 5 mg twice daily for the treatment of patients with platelet counts in the range of 50 to 100 x 10^9/L. Data from a retrospective observational analysis on the use of ruxolitinib provided through an individual patient supply program demonstrate that patients with intermediate-1 risk disease experience a comparable benefit from ruxolitinib therapy to patients with intermediate-2 and high risk disease.

INDICATIONS

Jakavi® is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients.

PRECAUTIONS

Decrease in blood cell count

Treatment with Jakavi can cause haematological adverse reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count must be performed before initiating therapy with Jakavi (for monitoring frequency see Dosage and Administration section).

It has been observed that patients with low platelet counts (<200X 10^9/L) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakavi. However, platelet transfusions may be required as clinically indicated (see Dosage and Administration and Adverse Effects sections).

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

Neutropenia (Absolute Neutrophil Count (ANC) <0.5X 10^9/L) was generally reversible and was managed by temporarily withholding Jakavi (see Dosage and Administration, and Adverse Effects sections).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see Dosage and Administration, and Adverse Effects sections).

Infections

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi for myelofibrosis. Attention should be given to the possibility of latent or active tuberculosis. Jakavi therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly (see Adverse Effects section).

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 Leukencephalopathy

Progressive Multifocal Leukencephalopathy (PML) has been reported with ruxolitinib treatment for myelofibrosis. Physicians should be alert for neuropsychiatric symptoms suggestive of PML.

Withdrawal Effects

Following interruption or discontinuation of ruxolitinib, symptoms of myelofibrosis may return over a period of approximately 1 week. There have been cases of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of ruxolitinib contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of ruxolitinib may be considered, although the utility of the tapering is unproven.

Effects on Fertility

There are no human data on the effect of ruxolitinib on fertility. In an animal study, ruxolitinib was administered to male rats prior to and throughout mating and to female rats prior to mating and up to the implantation day. Ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses up to 60 mg/kg/day. However, in female rats doses of greater than or equal to 30 mg/kg/day resulted in increased post-implantation

loss. The exposure (free AUC) at the dose of 30 mg/kg/day is approximately equivalent to the clinical exposure at the maximum recommended dose of 25 mg twice daily.

Women of child-bearing potential

Women of child-bearing potential must take appropriate precautions to avoid becoming pregnant during treatment. In case pregnancy occurs, risk/benefit evaluations must be carried out on an individual basis with careful counselling regarding potential risk to the fetus using the most recent data available.

Use in Pregnancy (Category C)

There are no adequate and well-controlled studies of Jakavi in pregnant women. Ruxolitinib and/or its metabolites crossed the placental barrier in pregnant rats. JAK2 is required for definitive erythropoiesis during embryogenesis. When administered during the period of organogenesis, ruxolitinib was embryolethal and fetotoxic in both rats and rabbits (increases in postimplantation loss and reduced fetal weights). Exposures (AUC) at the no effect level were subclinical. There was no evidence of teratogenicity. The use of Jakavi during pregnancy is not recommended.

Use in Lactation

Jakavi must not be used during breast-feeding 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. 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.

In a study in which pregnant rats were dosed with ruxolitinib from implantation through lactation at oral doses up to 30 mg/kg/day, there were no adverse effects on postnatal survival, pup development or pup reproductive function. Maternal exposure (AUC) at the highest dose level was subclinical.

Paediatric Use

The safety and efficacy of Jakavi in paediatric patients have not been established.

Use in the Elderly

No additional dose adjustments are recommended for elderly patients.

Genotoxicity

Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in an *in vitro* chromosomal aberration assay (cultural human peripheral blood lymphocytes) or an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of carcinogenicity was observed in a 6 month study in the Tg.rasH2 transgenic mouse model at oral doses of ruxolitinib up to 125 mg/kg/day, resulting in approximately 9 times the human exposure (AUC) at the maximum recommended dose of 25 mg twice daily.

INTERACTIONS WITH OTHER MEDICINES

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, ruxolitinib was not an inhibitor of the OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transporters at clinically-relevant concentration. Ruxolitinib is not a substrate for the P-glycoprotein transporter but was shown to be a weak inhibitor of this transporter. The effect of ruxolitinib on medicines which are substrates of P-glycoprotein are unknown.

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 Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)**:** in healthy subjects receiving ketoconazole, a strong CYP3A4 inhibitor, at 200 mg twice daily for four days, the AUC of Jakavi increased by 91% and the half-life was prolonged from 3.7 to 6.0 hours.

When administering Jakavi with strong CYP3A4 inhibitors the total daily dose of Jakavi should be reduced by approximately 50% (for monitoring frequency see Dosage and Administration section).

Patients should be closely monitored for cytopenias and dose titrated based on safety and efficacy (see Dosage and Administration section).

Other interactions to be considered

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)**:** in healthy subjects receiving erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for four days, there was a 27% increase in the AUC of Jakavi.

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

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

CYP3A4 inducers (such as, but not limited to, dexamethasone, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), rifapentine, St.John's wort (Hypericum perforatum))**:** Upon initiation of a CYP3A4 inducer, no dose adjustment is recommended. Patients should be closely monitored and the dose titrated based on safety and efficacy.

In healthy subjects receiving rifampin, a potent CYP3A4 inducer, at 600 mg once daily for ten days, the AUC of Jakavi following a single dose decreased by 71% and the half-life decreased from 3.3 to 1.7 hours. The relative amount of active metabolites increased in relation to parent compound.

Substances metabolised by CYP3A4: It cannot be excluded that ruxolitinib inhibits CYP3A4 in the intestine. Increased systemic exposure may be obtained for substances which are metabolised by CYP3A4, and particularly those that undergo extensive intestinal metabolism. Some sensitive CYP3A substrates include lovastatin, aprepitant, budesonide, conivaptan, darifenacin, darunavir, everolimus, sirolimus, and midazolam. Safety monitoring of orally administered CYP3A4 metabolised substances is advised when combined with ruxolitinib. The interaction is likely to be minimised if the time between co-administrations is kept as long as possible.

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

Drugs that inhibit P-glycoprotein include tacrolimus, cyclosporine, diltiazem, amiodarone, carvedilol, nifedipine, verapamil, ketoconazole, itraconazole, quinidine, ritonavir, saquinavir, nelfinavir, ranolazine valspodar and isradipine. 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.

No dose adjustment is recommended when Jakavi is co-administered with substances that interact with P-gp and other transporters.

Cytoreductive therapies: The concomitant use of cytoreductive therapies and Jakavi has not been studied. Some cytoreductive therapies include hydroxyurea, mercaptopurine, melphalan, chlorambucil and cytarabine. The safety and efficacy of this co-administration is not known.

ADVERSE EFFECTS

Summary of the safety profile

The safety profile of Jakavi has been assessed in 617 patients treated in 6 studies evaluating subjects with myelofibrosis, prostate cancer, multiple myeloma, essential thrombocythemia and polycythemia vera. In the clinical studies program the severity of adverse drug reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) defining grade 1=mild, grade 2= moderate, Grade 3=severe and grade 4=life-threatening or disabling.

In the two pivotal studies COMFORT-I and COMFORT-II, 301 patients had a median duration of exposure to Jakavi of 9.6 months (range 2 weeks to 17 months). The majority of patients (55.8%) were treated for at least 9 months, with 74 patients (24.6%) treated for 12 months or longer. Of the 301 patients, 111 (36.9%) had a baseline platelet count between 100X 10^9/L and 200X 10^9/L, and 190 (63.1%) had a baseline platelet count >200X 10^9/L [Table 3-5].

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

Haematological adverse reactions (any CTCAE grade) included anaemia (81.7%), thrombocytopenia (67.4%) and neutropenia (15.3 %).

Anaemia, thrombocytopenia and neutropenia are dose related effects.

The three most frequent non-haematological adverse reactions were bruising (19.3%), dizziness (14.3%) and headache (12.6%). The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (26.2%), raised aspartate aminotransferase (18.6%) and hypercholesterolaemia (16.6%).

In Phase 3 clinical studies discontinuation due to adverse events, regardless of causality was observed in 9.6% of patients.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (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 (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 3 Percentage of patients with adverse drug reactions in clinical studies[1)]

Adverse drug reactions and CTCAE grade	**Comfort 1**		**Comfort 2**		Total for Ruxolitinib N=301	Frequency category
	Ruxolitinib N=155	**Placebo N=151**	**Ruxolitinib N=146**	**Best available therapy N=73**		
	%	%	%	%	%	
Infections and infestations						
Urinary Tract infections[1]	9	5.3	14.4	6.8	11.6	Very Common
Herpes zoster[1]	1.9	0.7	5.5	0	3.7	Common
Tuberculosis	0.6	0	1.4	0	1	Common
Blood and lymphatic system disorders						
Anemia2						
CTCAE 3 grade 4 (<6.5g/dL)	11.0	2.6	8.2	9.6	9.6	Common
CTCAE grade 3 (<8.0 – 6.5g/dL)	31.6	12.6	30.1	11.0	30.9	Very common
Any CTCAE grade	81.9	41.7	81.5	49.3	81.7	Very common
Thrombocytopenia[2]						
CTCAE grade 4 (<25X 10^9/L)	3.9	0	2.1	2.7	3.0	Common
CTCAE grade 3 (50 – 25X 10^9/L)	9.0	1.3	6.2	4.1	7.6	Common
Any CTCAE grade	68.4	19.2	66.4	26.0	67.4	Very common
Neutropenia[2]						
CTCAE grade 4 (<0.5X 10^9/L)	1.9	1.3	2.7	1.4	2.3	Common
CTCAE grade 3 (<1 – 0.5X 10^9/L)	4.5	0.7	3.4	0	4.0	Common
Any CTCAE grade	18.1	4.0	12.3	8.2	15.3	Very common
Metabolism and nutrition disorders						
Weight gain[1]	7.1	1.3	9.6	0	8.3	Common
Hypercholesterolemia[2,4] Any CTCAE grade	17.4	0.7	15.8	6.8	16.6	Very common
Nervous system disorders						
Dizziness[1]	18.1	7.3	10.3	8.2	14.3	Very common
Headache[1]	14.8	5.3	10.3	4.1	12.6	Very common
Gastrointestinal disorders						
Flatulence1	5.2	0.7	1.4	0	3.3	Common
Hepatobiliary disorders						
Raised alanine aminotransferase[2, 5]						
CTCAE grade 3 (> 5x – 20 x ULN)	18.1	6.60	1.4	0	1.3	Common
Any CTCAE grade	27.1	7.9	25.3	6.8	26.2	Very common
Raised aspartate aminotransferase[2,5]						
Any CTCAE grade	18.1	6.6	19.2	2.7	18.6	Very common
Skin and subcutaneous tissue disorders						
Bruising[1]	23.2	14.6	15.1	5.5	19.3	Very common

1 Frequency is based on adverse event data.
2 Frequency is based on laboratory values.
-A subject with multiple occurrences of an ADR is counted only once in that ADR category.
-ADRs reported are on treatment or up to 28 days post treatment end date.
3 Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0;
Grade 1=mild, Grade 2= moderate, Grade 3=severe, grade 4=life-threatening or disabling.
4 In phase 3 clinical studies no CTCAE grade 3 or 4 hypercholesterolaemia was observed.

5 In phase 3 clinical studies no CTCAE grade 4 raised alanine aminotransferase was observed and no CTCAE grade 3 or 4 raised aspartate aminotransferase was observed.
ULN = upper limit of normal
-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.

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

Description of selected adverse drug reactions

Anaemia

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

In patients receiving Jakavi mean decreases in haemoglobin reached a nadir of approximately 15 to 20 g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 10 g/L below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomized, placebo controlled study (COMFORT-I), 59.4% of Jakavi treated patients and 37.1% of patients receiving placebo received red blood cell transfusions during randomized treatment. In the COMFORT-II study, the rate of packed red blood cell transfusions was 51.4% in the Jakavi arm and 38.4% in the best available therapy arm (BAT).

Thrombocytopenia

In the Phase 3 clinical studies, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50X 10^9/L was 14 days. Platelet transfusions were administered to 4.5% of patients receiving Jakavi and to 5.8% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100X 10^9/L to 200X 10^9/L before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200X 10^9/L (64.2% versus 35.4%).

Neutropenia

In the phase 3 clinical studies, in patients who developed grade 3 or 4 neutropenia, the median time of onset was 12 weeks. Dose holding or reductions due to neutropenia were reported in 1.3% of patients and 0.3% of patients discontinued treatment because of neutropenia.

Urinary tract infections

In phase 3 clinical studies grade 3 or 4 urinary tract infection was reported for 1.0% of patients. Urosepsis was reported in 1.0% of patients and kidney infection 1 patient.

Herpes zoster

In phase 3 clinical studies grade 3 or 4 herpes zoster was reported in 1 patient.

Increased systolic blood pressure

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

DOSAGE AND ADMINISTRATION

Monitoring instructions

Blood cell counts: a blood cell count must be performed before initiating therapy with Jakavi. Complete blood counts should be monitored every 2 to 4 weeks until doses are stabilized, and then as clinically indicated (see Precautions section).

Dose

Jakavi is given orally twice daily with or without food. The recommended starting dose is based on platelet count (Table 4).

Table 4 Recommended Jakavi Starting Dose

Platelet Count	Starting Dose
50-100 x 10^9/L	5 mg bd
100-200 x 10^9/L	15 mg bd
> 200 x 10^9/L	20 mg bd

The dose is then titrated based on safety and efficacy. The maximum dose of Jakavi is 25 mg twice daily. If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

Treatment may be continued as long as the benefit- risk ratio remains positive.

There are limited data on initiating Jakavi in patients with platelet counts of 50-100 X 10^9/L. Jakavi should only be used in these patients if hepatic function is normal and renal function is

normal or mildly impaired. The Jakavi dose should be titrated cautiously based on response and blood cell counts.

Dose Reduction

The Jakavi dose should be reduced if the platelet count decreases below 100 x 10^9/L (Table 5).

Jakavi treatment should be interrupted if the platelet count decreases below 50X 10^9/L or the absolute neutrophil count decreases below 0.5X 10^9/L. After recovery of platelet and neutrophil counts above these levels, Jakavi may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of blood cell counts.

Table 5: Dosing Recommendations for Thrombocytopenia

	Dose at Time of Platelet Decline				
Platelet Count	**25 mg twice daily**	**20 mg twice daily**	**15 mg twice daily**	**10 mg twice daily**	**5 mg twice daily**
	New Dose	**New Dose**	**New Dose**	**New Dose**	**New Dose**
100 to less than 125 X 10^9/L	20 mg twice daily	15 mg twice daily	No Change	No Change	No Change
75 to less than 100 X 10^9/L	10 mg twice daily	10 mg twice daily	10 mg twice daily	No Change	No Change
50 to less than 75 X 10^9/L	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No Change
Less than 50 X 10^9/L	Hold	Hold	Hold	Hold	Hold

Dose modifications based on Response

If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Discontinue treatment after 6 months if there is no spleen size reduction or symptom improvement since initiation of therapy with Jakavi.

Based on limited clinical data, long-term maintenance at a 5 mg twice daily dose has not shown responses and continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks.

Dose adjustment with concomitant strong CYP3A4 Inhibitors:

When Jakavi is administered with strong CYP3A4 inhibitors the total daily dose of Jakavi should be reduced by approximately 50% either by decreasing the twice daily dose or by

decreasing the frequency of dosing to the corresponding once daily dose when twice daily dosing is not practical.

More frequent monitoring of haematology parameters and clinical signs and symptoms of Jakavi related adverse reactions is recommended upon initiation of a strong CYP3A4 inhibitor.

Patients with Renal Impairment

In patients with moderate to severe renal impairment (creatinine clearance (Clcr) less than 60mL/min) the recommended starting dose based on platelet count should be reduced by approximately 50%. Patients diagnosed with moderate to severe renal impairment while receiving Jakavi should be carefully monitored and may need to have their doses reduced to avoid adverse drug reactions.

There are limited data to determine the best dosing options for patients with end-stage renal disease on dialysis. Available data in this population suggest that patients on dialysis should be started on an initial single dose of 15 mg or 20 mg based on platelet counts with subsequent single doses only after each dialysis session, and with careful monitoring of safety and efficacy (see Pharmacology section). There are no data for patients undergoing peritoneal dialysis or continuous venovenous haemofiltration. Jakavi should be avoided in patients with end stage renal disease (CrCl less than 15 mL/min) not undergoing dialysis and in patients with moderate to severe renal impairment with platelet counts less than 100×10^9/L.

Patients with Hepatic Impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50%. Patients diagnosed with hepatic impairment while receiving Jakavi should be carefully monitored and may need to have their dose reduced to avoid adverse drug reactions.

Jakavi should be avoided in patients with hepatic impairment with platelet counts less than 100×10^9/L.

Elderly Patients

No additional dose adjustments are recommended for elderly patients.

OVERDOSAGE

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

Hemodialysis is not expected to enhance the elimination of Jakavi.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

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

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

20 mg tablet: Elongated curved white to almost white tablets of approximately 16.5 x 7.4 mm with "NVR" debossed one one side and "L20" debossed on the other side,.

Jakavi 5 mg, 15 mg and 20 mg tablets: bottles containing 60 tablets

Jakavi 5 mg, 15 mg and 20 mg tablets: blisters containing 14, 28, 56, 112, 168, 224 tablets

Pack sizes: Not all pack sizes may be marketed.

Storage: Store below 30^{o}C

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

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54 Waterloo Road

North Ryde NSW 2113

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POISON SCHEDULE OF THE MEDICINE

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