Summary of the risk management for Jakavi® (ruxolitinib)

This is a summary of the risk management plan (RMP) for Jakavi. The RMP details important risks of Jakavi, how these risks can be minimized and how more information will be obtained about Jakavi's risks and uncertainties (missing information).

Jakavi's summary of product information (SmPC) and its package leaflet (PL) give essential information to health care professionals (HCPs) and patients on how Jakavi should be used.

This summary of the RMP for Jakavi should be read in the context of all this information including the AR of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Jakavi's RMP.

I. The medicine and what it is used for

Jakavi is a selective inhibitor of the Janus kinases. Jakavi is authorized for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (MF) (also known as chronic idiopathic MF), post-polycythemia vera (PV)-MF or post-essential thrombocythemia-MF. Jakavi is indicated for the treatment of adult patients with PV who are resistant to or intolerant of hydroxyurea (HU). Currently, ruxolitinib is also indicated for the treatment of patients with graft versus host disease (GvHD) aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. Jakavi contains "ruxolitinib" as the active ingredient and it is given by oral route.

The recommended starting dose of Jakavi in MF is 15 mg given orally b.i.d. for patients with a platelet count between 100000/mm^3 and 200000/mm^3 and 20 mg b.i.d. for patients with a platelet count of > 200000/mm^3. The recommended starting dose in patients with platelet counts between 75000/mm^3 and < 100000/mm^3 and between 50000/mm^3 and < 75000/mm^3 is 10 mg b.i.d. and 5 mg b.i.d., respectively. The patients should be titrated cautiously.

The recommended starting dose of Jakavi in PV is 10 mg given orally b.i.d. There is limited information to recommend a starting dose for patients with platelet counts between 50000/mm^3 and < 100000/mm^3. The maximum recommended starting dose in these patients is 5 mg b.i.d. and the patients should be titrated cautiously.

The recommended starting dose of ruxolitinib in acute GvHD (aGvHD) and chronic GvHD (cGvHD) is 10 mg given orally b.i.d.

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50000/mm^3 or absolute neutrophil count (ANC) less than 500/mm^3. In PV, treatment should also be interrupted when hemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg b.i.d. and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell (WBC) count differential.

Dose reductions should be considered if the platelet count decreases below 100000/mm^3, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if hemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

Dose reductions and temporary interruptions may be needed in GvHD patients with thrombocytopenia, neutropenia, and elevated total bilirubin after standard supportive therapy including growth factors, anti-infective therapies and transfusions.

One dose level reduction step is recommended (10 mg b.i.d. to 5 mg b.i.d. or 5 mg b.i.d. to 5 mg once daily). In patients who are unable to tolerate ruxolitinib at a dose of 5 mg once daily, treatment should be interrupted.

In GvHD, tapering of ruxolitinib may be considered in patients with a response and after having discontinued corticosteroids. 50% dose reduction every 2 months is recommended. If signs or symptoms of GvHD reoccur during or after the taper of ruxolitinib, re-escalation of treatment should be considered.

Further information about the evaluation of Jakavi's benefits can be found in Jakavi's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002464/WC500133225.pdf.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Jakavi together with measures to minimize such risks and the proposed studies for learning more about Jakavi's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures. There are no additional risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Jakavi is not yet available, it is listed under 'missing information' below:

- Safety in pediatric patients ≥12 years (GvHD only).

II.A: List of important risks and missing information

Important risks of Jakavi are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Jakavi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

Important identified risk	Serious infections
Important potential risk	Developmental toxicity
Missing information	Safety in pediatric patients ≥ 12 years (GvHD only)

II.B: Summary of important risks

Table 2 Important identified risk: Serious infections

Evidence for linking the risk to the medicine	The frequently reported infections include: viral reactivation of Herpes zoster (HZ) (shingles), Urinary tract infection (UTI). Infections were frequently reported cause of death due to adverse events (AEs) in patients with MF. The frequency and severity of infections appear to be higher in MF patients than in PV patients. In GvHD indication, as expected in this patient population, infections were frequently reported AEs; cytomegalovirus infections including reactivation and sepsis are common infections in aGvHD and pneumonia and upper respiratory tract infections are common infections in cGvHD.
Risk factors and risk groups	Low neutrophil count, pre-existing comorbidities chronic obstructive pulmonary disease, asthma, diabetes, co-medication (corticosteroids), higher dose, lack of dose adjustment if strong cytochrome P450 3A4 inhibitors or fluconazole are used or the patient develops hepatic impairment, moderate or severe renal impairment (creatinine clearance < 30 mL/min) or has end stage renal failure requiring hemodialysis.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.4: Precaution for monitoring, treatment and description of risk factors and nature of risk. Section 4.8: The adverse drug reactions (ADRs) of UTI, HZ, pneumonia, tuberculosis and sepsis are listed. **Additional risk minimization measures** None

Table 3	**Important potential risk: Developmental toxicity**
Evidence for linking the risk to the medicine	Myelofibrosis or PV is mainly a condition of the adult population; the median age of patients recruited in Phase III studies was about 66 years. Cases of childhood age are very rare. The number of female patients of child-bearing potential receiving Jakavi is therefore expected to be limited. In the pivotal studies, 6 female patients, ≤ 45 years representing 1.1% of the total population were enrolled. Due to the severity of the oncological condition the fertility rate of these elderly female patients is expected to be low. There are no data from the use of Jakavi in pregnant women with PV. Animal studies have shown that Jakavi is embryotoxic (causing harm to the embryo) and fetotoxic (causing harm to the fetus). 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 counseling regarding potential risks to the fetus.
Risk factors and risk groups	Women of child-bearing potential not using effective contraception, breast-feeding women and children.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.1 Section 4.2 Section 4.3 Section 4.6 Section 5.3 There are no data from the use of Jakavi in pregnant women. **Additional risk minimization measures** None

Table 4	**Missing information: Safety in pediatric patients ≥ 12 years (GvHD only)**
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2: The ruxolitinib dose in pediatric patients with GvHD aged 12 years and older is the same as in adults. **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study INC424F12201: This is a study of pharmacokinetics, activity and safety of ruxolitinib in pediatric patients with grade 2 to 4 in aGvHD. Study INC424G12201: This is a study of activity, safety and pharmacokinetics in pediatric subjects with moderate and severe cGvHD after allogeneic stem cell transplantation (allo-SCT). See Section II.C of this summary for an overview of the post-authorization development plan.

II.C: Post-authorization development plan

II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Jakavi.

II.C.2. Other studies in post-authorization development plan

Table 5 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CINC424F12201 Open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric patients with grade 2 to 4 aGvHD after allo-SCT.	The rationale of the study is based on current knowledge of aGvHD pathophysiology and published studies showing that ruxolitinib impairs antigen presenting cell (APC) function, inhibits donor T cell proliferation, suppresses adverse cytokine production, and improves survival and disease manifestations in GvHD mouse models. Further, published data has shown that ruxolitinib has evidence of clinical efficacy when added to immunosuppressive therapy in patients with steroid refractory aGvHD. Clinical studies using ruxolitinib (10 mg b.i.d.) alone or in comparison to best available therapy (BAT) are currently underway in the steroid refractory (SR)-aGvHD setting for adult patients and adolescents ≥ 12 years of age. Recent data with ruxolitinib in SR-aGvHD pediatric patients (ages 1.6 years -16.4 years) have shown encouraging overall response rate compared to corticosteroids +/- calcineurin inhibitor alone.
Study CINC424G12201 Open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric subjects with moderate and severe cGvHD after allo-SCT.	The rationale of the study is based on current knowledge of cGvHD pathophysiology and published studies showing that ruxolitinib impairs APC function, inhibits donor T cell proliferation, suppresses adverse cytokine production, and improves survival and disease manifestations in GvHD mouse models. This signaling cascade in cGvHD determined in the mouse model and adult subjects with cGvHD, is expected to be the same in pediatric subjects < 12 years of age as compared to subjects ≥ 12 years of age. Further, published data has shown that ruxolitinib has evidence of clinical efficacy when added to immunosuppressive therapy in subjects with SR-cGvHD. Clinical studies using ruxolitinib (10 mg b.i.d.) alone or in comparison to BAT are currently underway in the SR-cGvHD setting for adult patients and adolescents ≥ 12 years of age. Despite children being at a lower risk of developing cGvHD than adults, the incidence of cGvHD in the pediatric population is substantial and has increased recently in association with the expanded use of peripheral blood stem cells and unrelated donors.