Jakavi® (ruxolitinib) in Myelofibrosis

Jakavi® is the first JAK 1 and JAK 2 inhibitor approved in more than 80 countries, including countries in the European Union, Canada, Japan and countries in Asia, Latin and South America, for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF). Additional global regulatory approvals in myelofibrosis are pending.

How does Jakavi work in myelofibrosis?

- Myelofibrosis develops when uncontrolled signaling in the JAK pathway – which regulates blood cell production – causes the body to make blood cells that do not work properly, which scars the bone marrow and results in an enlarged spleen and other severe complications.
- Patients may also suffer debilitating symptoms including fever, extreme fatigue, intractable pruritus (itchiness), night sweats, weight loss, bone or muscle pain, poor quality of life and shortened survival.
- Research has indicated that Jakavi (ruxolitinib) directly targets the underlying mechanism of disease, and in clinical trials it significantly reduced the size of the spleen in patients with myelofibrosis and relieved symptoms regardless of JAK mutational status, disease subtype, or any prior treatment, including hydroxyurea.

The approval of Jakavi in myelofibrosis was based on the pivotal Phase III data from the randomized, double-blind, placebo-controlled multi-center COMFORT-I trial and randomized, open-label, multi-center COMFORT-II trial (GOntrolled MyeoloFibrosis Study with ORal JAK Inhibitor Therapy).

- COMFORT-I included 309 patients with primary MF, PPV-MF or PET-MF in 89 study locations in Canada, Australia and the United States. Half of the patients (155) received Jakavi twice daily and half (154) received placebo. The study consisted of a randomized treatment phase and an optional extension phase, during which patients on placebo could begin receiving Jakavi open label.
- COMFORT-II included 219 patients with primary MF, PPV-MF or PET-MF in 56 study locations in Europe. Two-thirds (146 patients) received Jakavi twice daily and one-third (73 patients) received conventional therapy, which is any commercially available agent (such as monotherapy or in combination) or no therapy at all. The trial consisted of a randomized treatment phase and an optional extension phase that consisted of a crossover control group.

Primary Analysis of COMFORT-I and COMFORT-II

- Chronic inflammation through elevated cytokine levels is one of the primary consequences of dysregulated JAK 1 and JAK 2 signaling, and may be a major contributor to morbidity and mortality of patients with myelofibrosis. In COMFORT-I, Jakavi was shown to alter the clinical course of myelofibrosis by reversing symptom progression and reducing spleen volume by 35% in 41.9% of patients at 24 weeks from baseline compared to 0.7% of patients in the placebo group (p<0.001), thus improving quality of life and potentially impacting overall survival by reducing risk of death.
- In COMFORT-II, a pivotal Phase III trial, continuous Jakavi therapy provided a marked and durable improvement in overall quality of life measures, functioning and symptoms including volumetric spleen-size reduction of 35% or greater in 28% of patients compared to 0% of patients treated with conventional therapy at 48 weeks (p<0.001). Improvement of symptoms included: loss of appetite, dyspnea (shortness of breath), fatigue, insomnia and pain, compared to worsening of symptoms in patients treated with conventional therapy.

Dosing in myelofibrosis

- Jakavi is an orally administered treatment and the recommended starting dose in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm³ and 200,000/mm³ and 20 mg twice daily for patients with a platelet count of >200,000/mm³. The maximum dose of Jakavi is 25 mg twice daily.
- There is limited information to recommend a starting dose for myelofibrosis patients with platelet counts between 50,000/mm³ and <100,000/mm³. The maximum recommended starting dose in these patients is 5 mg twice daily and patients should be titrated cautiously.
- A complete blood count must be performed before initiating therapy with Jakavi. Complete blood counts should be monitored as clinically indicated and dosing adjusted as required.
- A dose modification is recommended when administering Jakavi with strong CYP3A4 inhibitors or in patients with hepatic impairment or severe renal impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.
- Following interruption or discontinuation of Jakavi, symptoms may return. Unless abrupt discontinuation is required, gradual tapering of the dose should be considered.

Adverse Events in myelofibrosis

The most frequently reported hematologic adverse reactions with Jakavi in myelofibrosis were anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (15.6%). Hematologic reactions were generally dose-related effects and manageable through dose reductions and/or transfusions, and such reactions rarely led to discontinuation. The three most frequent nonhematologic adverse reactions were bruising (21.3%), dizziness (15%) and headache (13.9%).
About Jakavi
Jakavi (ruxolitinib) is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases. Jakavi is approved by the European Commission for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea and for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocytopenia myelofibrosis. Jakavi is approved in more than 80 countries for patients with myelofibrosis, including countries in the European Union, Canada, Japan and countries in Asia, Latin and South America. Additional worldwide regulatory filings are underway in myelofibrosis and PV.

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization outside the United States. Jakavi is marketed in the United States by Incyte Corporation as Jakafi® for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea and for the treatment of patients with intermediate or high-risk myelofibrosis.

The recommended starting dose of Jakavi in PV is 10 mg given orally twice daily. The recommended starting dose of Jakavi in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000 cubic millimeters (mm³) and 200,000 mm³, and 20 mg twice daily for patients with a platelet count of >200,000 mm³. Doses may be titrated based on safety and efficacy. There is limited information to recommend a starting dose for myelofibrosis and PV patients with platelet counts between 50,000/mm³ and <100,000/mm³. The maximum recommended starting dose in these patients is 5 mg twice daily, and patients should be titrated cautiously.

Jakavi is a registered trademark of Novartis AG in countries outside the United States. Jakafi is a registered trademark of Incyte Corporation. The safety and efficacy profile of Jakavi has not yet been established outside the approved indications.

Jakavi Important Safety Information for Treatment of Myelofibrosis (MF) and Polycythemia Vera (PV)
Jakavi can cause serious side effects, including a decrease in blood cell count and infections. Complete blood count monitoring is recommended. Dose reduction or interruption may be required in patients with any hepatic impairment or severe renal impairment or in patients developing hematologic adverse reactions such as thrombocytopenia, anemia and neutropenia. Dose reductions are also recommended when Jakavi is co-administered with strong CYP3A4 inhibitors or fluconazole. Use of Jakavi during pregnancy is not recommended, and women should avoid becoming pregnant during Jakavi therapy. Women taking Jakavi should not breast feed.

Progressive multifocal leukoencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. Hepatitis B viral load (HBV-DNA titer) increases have been reported in patients with chronic HBV infections. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Non-melanoma skin cancer (NMSC) has been reported in Jakavi treated patients. Periodic skin examination is recommended. Very common adverse reactions in MF (>10%) include urinary tract infections, anemia, thrombocytopenia, neutropenia, hypercholesterolemia, dizziness, headache, alanine aminotransferase increased, aspartate aminotransferase increased, bruising and weight gain. Common adverse reactions in MF (1 to 10%) include herpes zoster and flatulence. Uncommon adverse reactions in MF include tuberculosis. Very common adverse reactions in PV (>10%) include anemia, thrombocytopenia, hypercholesterolemia, hypertiglycieridemia, dizziness, alanine aminotransferase increased and aspartate aminotransferase increased. Common adverse reactions in PV (1 to 10%) include urinary tract infections, herpes zoster, weight gain, constipation and hypertension.

Please see full Prescribing Information available at www.jakavi.com.

References