Jakavi® (ruxolitinib) in Myelofibrosis

Jakavi® is the first JAK 1 and JAK 2 inhibitor approved in more than 50 countries, including the European Union, Canada and some 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 regulatory approvals are pending.

How does it work?

- Myelofibrosis develops when uncontrolled signaling in the JAK pathway – which regulates blood cell production – causes scarring in the bone marrow and faulty blood cell production, resulting in an enlarged spleen when it takes responsibility for blood cell creation. 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 (CONTROLled Myelofibrosis Study with ORal JAK Inhibitor Therapy).

- COMFORT-I included 309 patients with primary MF, PPV-MF or PET-MF in 89 study locations in the United States, Canada and Australia. 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 myelofibrosis, 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.

- 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

- Jakavi is an orally administered treatment and the recommended starting dose 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 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

The most frequently reported hematologic adverse reactions with Jakavi 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%).
Jakavi® Important Safety Information

The recommended starting dose for Jakavi is 15 mg twice daily for patients with a platelet count between 100,000 cubic millimeters (mm$^3$) and 200,000 mm$^3$, and 20 mg twice daily for patients with a platelet count of >200,000 mm$^3$. Doses may be titrated based on safety and efficacy. There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm$^3$ and <100,000/mm$^3$. The maximum recommended starting dose in these patients is 5 mg twice daily and patients should be titrated cautiously

Jakavi® can cause serious side effects, including a decrease in blood cell count and infections. Complete blood counts monitoring is recommended. Progressive multifocal leukencephalopathy (PML) has been reported. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. Dose reduction or interruption may be required in patients with severe hepatic or 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.

The most common adverse drug reactions, occurring at any level of severity (incidence >10%) are urinary tract infections, anemia, trombocytopenia, neutropenia, hypercholesterolaemia, dizziness, headache, alanine aminotransaminase increased, asparte aminotransferase increased, bruising, bleeding and increased blood pressure. Other common adverse drug reactions (incidence 1 to 10%) are herpes zoster, weight gain, flatulence and tuberculosis (1%)..

Please see full prescribing information available at www.jakavi.com.

An Important Note

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization outside the United States. Both the European Commission and the US Food and Drug Administration (FDA) granted ruxolitinib orphan drug status for myelofibrosis. Jakavi is marketed in the United States by Incyte Corporation under the name Jakafi® for the treatment of patients with intermediate or high-risk myelofibrosis.

References