Health Alliance: Jakafi™ (ruxolitinib)

PROGRAM RATIONALE
Client Requested: The intent of the criteria is to ensure that patients follow selection elements established by Health Alliance medical policy for Jakafi (ruxolitinib).

FDA-APPROVED INDICATION
Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.1

CLINICAL BACKGROUND
Myelofibrosis (MF) is part of a related group of conditions referred to as myeloproliferative neoplasms (MPNs) of hematopoietic stem cells which lead to an inappropriate release of cytokines, fibrosis of the bone marrow and extramedullary hematopoiesis.2 MF may present as a primary condition or may develop late in the course of essential thrombocythemia (ET) or polycythemia vera (PV), the two most common and benign MPNs.2,3 Other classic MPNs include chronic myeloid leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, and mast cell disease.4 Among these MPNs, PV, ET, and primary MF (PMF) are BCR-ABL1-negative and screening for the BCR-ABL gene to rule out other secondary causes of myelofibrosis such as CML may be recommended.4,5 PMF is uncommon, affecting about 2 out of 1,000,000 people annually.6 About 10 to 15% of patients with PV or ET transform into MF.6

MF is characterized by progressive anemia, bone marrow fibrosis, splenomegaly and a constellation of debilitating symptoms such as fatigue, abdominal discomfort, bone and muscle pain, night sweats, and weight loss which significantly impact quality of life.7,8 MF can also transform into acute myeloid leukemia (AML) leading to premature death.7,8 The median survival time after a diagnosis of MF is about 5 years or less, though some people live much longer.9,10 Survival in MF is related to the number of prognostic risk factors and ranges from 2 to 4 years among patients with two or more risk factors (intermediate-2 or high risk) to 8 to 11 years among patients with no risk or one risk factor (intermediate-1 or low risk).7,8

Currently, there is no curative therapy for MF except for allogeneic stem cell transplantation (ASCT).8,10 However, ASCT is not an option for most patients.8 Also, ASCT is complicated by relatively high treatment-related mortality and morbidity.8,10 Thus, the main treatment goal of MF has been focused on relieving symptoms related to massive splenomegaly and anemia.2,3 To date, there were no FDA-approved therapies for MF.5 Therapies that are currently available such as hydroxyurea, erythropoietin, androgens, decitabine, and thalidomide are being used in an off-label setting.7,8,10

It has been found that MF is associated with mutations in the Janus Associated Kinase 2 (JAK2) gene, most commonly JAK2-V617F.2,2 The JAK2 V617F mutation is present in more than 90% of patients with PV and approximately 60% of patients with primary MF or ET.3,10 Some clinical signs of the disease, such as anemia and splenomegaly, and the risk of transformation to AML have been related to JAK2 V617F mutational status or the JAK2 V617F allele burden.1 On November 16, 2011, the Food and Drug Administration approved Jakafi (ruxolitinib), the first drug approved to specifically treat patients with intermediate or high risk MF. Jakafi inhibits both JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function.1

The safety and efficacy of Jakafi was evaluated in two randomized Phase 3 studies (Studies 1 and 2).7 All patients had an enlarged spleen and risk category of intermediate 2 or high risk. Study 1 was a double-blind, randomized, placebo-controlled study with 309 patients who were refractory to or were not candidates for available therapy. Patients were randomized to receive either Jakafi or placebo. The primary efficacy endpoint was the proportion of patients achieving at least 35% reduction in spleen volume from baseline to week 24. The secondary endpoints were duration of a 35% or more reduction in spleen volume and proportion of patients with at least 50% reduction in myelofibrosis-related symptoms from baseline to week 24. Study 2 was an open-label, randomized study with 219 patients who were randomized to receive either Jakafi or best available therapy (e.g., hydroxyurea, a chemotherapy agent, or glucocorticoids). The primary and secondary endpoints were the proportion of patients achieving at least 35% reduction in spleen volume from baseline to week 48 and to week 24, respectively. In both studies, a significantly higher proportion of patients in the Jakafi group achieved a 35% or more reduction in spleen volume from baseline. Also,
a higher proportion of patients in the Jakafi group had a 50% or more reduction in their myelofibrosis-related symptoms as compared to placebo.

SAFETY
Treatment with Jakafi can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia. Complete blood counts must be performed before starting Jakafi therapy and should be monitored as clinically indicated and as dosing is adjusted. Patients with platelet counts of less than 200 x 10^9/L at the start of therapy are more likely to develop thrombocytopenia during treatment. Patients with a platelet count of 100 x 10^9/L to 200 x 10^9/L before starting Jakafi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 x 10^9/L (16.5% vs. 7.2%). Thrombocytopenia and neutropenia are generally reversible and may be managed by temporarily withholding Jakafi doses. Thrombocytopenia and anemia may also be managed by blood transfusions if indicated. Patients should be assessed for signs and symptoms of infection and any active serious infections should be resolved prior to starting therapy with Jakafi.

JAKAFI ALGORITHM

ABBREVIATIONS
ET = essential thrombocythemia
PV = polycythemia vera
REFERENCES


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The Participating Group signed below hereby accepts and adopts as its own the criteria for use with Specialty Guideline Management, as administered by CVS Caremark.

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Signature                       Date

Client Name