Medication Policy Manual

**Policy No:** dru268

**Topic:** Jakafi®, ruxolitinib

**Date of Origin:** January 13, 2012

**Committee Approval Date:** January 13, 2017

**Next Review Date:** January 2018

**Effective Date:** February 1, 2017

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

*Benefit determinations should be based in all cases on the applicable contract language.* To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Ruxolitinib (Jakafi) is a self-administered oral Janus-associated kinase 1 (JAK1) and JAK2 inhibitor used in the treatment of myelofibrosis and polycythemia vera (PV).
Policy/Criteria

I. Most contracts require prior authorization approval of ruxolitinib (Jakafi) prior to coverage. Ruxolitinib (Jakafi) may be considered medically necessary in patients when either criterion A or B below is met:

A. There is a diagnosis of myelofibrosis, including but not limited to primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis.

OR

B. There is a diagnosis of polycythemia vera (PV) when therapy with hydroxyurea is contraindicated or prior therapy with hydroxyurea has been ineffective or not tolerated as defined by one or more of the following criteria 1 through 5 below:

1. Need for more than four phlebotomies in 12 months to keep hematocrit below 45% after three months of hydroxyurea at maximally tolerated doses.

OR

2. Uncontrolled myeloproliferation defined as elevated white blood cell (WBC) count (>10,000/mm³) and elevated platelet count (>400,000/mm³) after three months of hydroxyurea at maximally tolerated doses.

OR

3. Worsening function due to disease.

OR

4. Absolute neutrophil count < 1,000/mm³, platelet count < 100,000/mm³, or hemoglobin < 10 g/dL at the lowest dose of hydroxyurea required to achieve a clinical or hematological response.

OR

5. Toxicities or adverse reactions to hydroxyurea (e.g. cutaneous vasculitic toxicities, gastrointestinal symptoms, pneumonitis, fever).

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers ruxolitinib (Jakafi) to be a self-administered medication.

B. When prior authorization is approved, ruxolitinib (Jakafi) may be authorized in quantities of up to 60 tablets per month.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
III. Ruxolitinib (Jakafi) is considered investigational when used for all other conditions including but not limited to:

- A. Acute leukemias
- B. Adult T-cell leukemia
- C. Breast cancer
- D. Chronic myelogenous leukemia
- E. Graft-versus-host Disease
- F. Multiple myeloma
- G. Myelodysplastic syndrome
- H. Non-Hodgkin lymphoma
- I. Pancreatic cancer
- J. Prostate cancer
- K. Psoriasis

Position Statement

- Ruxolitinib (Jakafi) is an oral Janus-associated kinase 1 (JAK1) and JAK2 inhibitor that is used in the treatment of myelofibrosis and polycythemia vera (PV). It inhibits overactive JAK 1 and JAK2 to decrease inflammatory cytokine signaling and overproduction of blood cells.

- Treatments for myelofibrosis are generally palliative and are directed against specific symptoms. Therapies include hydroxyurea; immunosuppressants, such as steroids and thalidomide; androgens; and etanercept (Enbrel). There are no large, well-conducted clinical trials for any of these agents in the treatment of myelofibrosis.

- There is moderate certainty that ruxolitinib (Jakafi) improves splenomegaly and symptoms associated with myelofibrosis; however, the extent of symptom improvement is uncertain.

- To date, no medication therapy has been shown to improve survival in patients with myelofibrosis. [1]

- The current standard of care for PV is phlebotomy which is done to remove excess red blood cells and lower blood viscosity. The goal is to keep the hematocrit below 45% in men and 42% in women. In patients at high risk for thrombosis, phlebotomy should be supplemented with the use of a myelosuppressive agent (hydroxyurea is preferred over an alkylating agent or interferon alpha). [2]

- Ruxolitinib (Jakafi) is approved for use as a second-line option for patients who have not responded to, or who cannot tolerate, hydroxyurea.

- In clinical trials, hydroxyurea ineffectiveness was defined as the need for phlebotomy to keep hematocrit < 45% after three months of maximally tolerated doses of hydroxyurea, uncontrolled myeloproliferation (i.e. elevated white WBC count and elevated platelet count), or worsening disease-related signs and symptoms (e.g. increasing splenomegaly). [3]
Hydroxyurea intolerance was defined as an absolute neutrophil count < 1,000/mm³, platelet count < 100,000/mm³, or hemoglobin < 10 g/dL at the lowest dose of hydroxyurea required to achieve a clinical or hematological response, or toxicities or adverse reactions to hydroxyurea (e.g. cutaneous vasculitic toxicities, gastrointestinal symptoms, pneumonitis, fever). [3]

It is estimated that 25% of patients with PV will develop resistance to or intolerance of hydroxyurea. [4]

To date, no medication, including ruxolitinib (Jakafi), has been shown to improve survival or lower the risk of leukemic transformation in PV.

Ruxolitinib (Jakafi) is relatively well tolerated with dose-related bone marrow suppression as its primary toxicity. Dose adjustments are necessary for thrombocytopenia and when concomitantly administered with strong CYP3A4 inhibitors.

Although ruxolitinib (Jakafi) is being studied in a variety of other conditions, there is currently no high-quality published clinical trial evidence supporting its safety or efficacy in these settings. [5]

Clinical Efficacy

MYELOFIBROSIS

The efficacy of ruxolitinib (Jakafi) for myelofibrosis is based on two phase III, randomized controlled trials in patients with intermediate- to high-risk myelofibrosis.

* One double-blinded randomized controlled trial evaluated the effects of ruxolitinib (Jakafi) on reduction in spleen volume and patient-reported myelofibrosis symptoms relative to placebo [COMFORT-1 trial]. The primary endpoint was reached in 41.9% of patients in the ruxolitinib (Jakafi) group vs 0.7% in the placebo group (p < 0.001). [6]

* A second open-label, randomized controlled trial evaluated the effects of ruxolitinib (Jakafi) on reduction in spleen volume relative to best available therapy (BAT), which may have included hydroxyurea, glucocorticoids, epoetin alfa, immunomodulators, or no medication therapy [COMFORT-2 trial]. At week 48, 28% of patients in the ruxolitinib (Jakafi) group had at least a 35% reduction in spleen volume vs 0% in the BAT group. [7]

* Neither of these studies was able to show a short-term improvement in overall survival for patients treated with ruxolitinib (Jakafi). Long-term extensions have demonstrated significant survival advantages for ruxolitinib (Jakafi) over placebo or BAT; however, because of the crossover nature of the COMFORT trials and the use of historical controls for determining long-term survival, the precise survival advantage remains unknown. [6-9]
The National Comprehensive Cancer Network (NCCN) Myeloproliferative Neoplasms guideline stratifies choice of treatment by severity of disease (i.e. mild, intermediate, and severe). Ruxolitinib (Jakafi) is among the recommended treatment options for symptomatic patients within each risk stratification.\textsuperscript{[10]}

POLYCYTHEMIA VERA (PV)

The efficacy of ruxolitinib (Jakafi) for PV is based on a phase III, open-label, randomized study (RESPONSE trial) in 222 patients with PV who were resistant to or intolerant of hydroxyurea, required phlebotomy, and exhibited splenomegaly.\textsuperscript{[11]}

* Subjects received ruxolitinib (Jakafi) or best available therapy (e.g. hydroxyurea, interferon, anagrelide, pipobroman, lenalidomide/thalidomide, observation) for 32 weeks.

* A significantly larger proportion of patients in the ruxolitinib (Jakafi) group achieved the primary endpoint, defined as having achieved both hematocrit control (absence of phlebotomy eligibility from week 8 through week 32) and spleen volume reduction (a greater than or equal to 35% reduction from baseline in spleen volume at week 32), compared to best available therapy (21% vs < 1%, respectively).

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.

\textit{Dosing considerations} \textsuperscript{[12]}

- Ruxolitinib (Jakafi) is available as 5 mg, 10 mg, 15 mg, 20 mg and 25 mg oral tablets.

- The FDA-recommended starting dose for myelofibrosis is 5 mg, 15 mg or 20 mg twice daily and is based on platelet count.

- Dose reductions for myelofibrosis should be considered for a platelet count of less than 125 x 10\textsuperscript{9}/L and for concomitant administration with strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole).

- The FDA-recommended starting dose for PV is 10 mg twice daily.

- Dose reductions for PV should be considered based on hemoglobin and platelet count decreases.

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\textbf{Cross References} & & \\
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None & & \\
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\textbf{Codes} & \textbf{Number} & \textbf{Description} \\
\hline
ICD-10 & D75.81 & Myelofibrosis \\
ICD-10 & D45 & Polycythemia vera \\
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References


Revision History

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<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
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<tbody>
<tr>
<td>1/13/2017</td>
<td>No criteria changes with this annual update.</td>
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<tr>
<td>1/8/2016</td>
<td>Added Graft-versus-host disease as an investigational indication.</td>
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