Jakafi® ruxolitinib (tablets)

SR Acute GVHD

Indications and Usage

Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.[1]

Steroid-Refractory Acute GVHD and the Role of Jakafi

Important Safety Considerations

- Treatment with Jakafi can cause thrombocytopenia, anemia, and neutropenia. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. In patients with cytopenias, consider dose reductions, temporarily interrupting Jakafi, or transfusions, as clinically indicated
- Serious bacterial, mycobacterial, fungal, and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Evaluate patients prior to and while receiving Jakafi for risk factors and signs and symptoms of infection, and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines

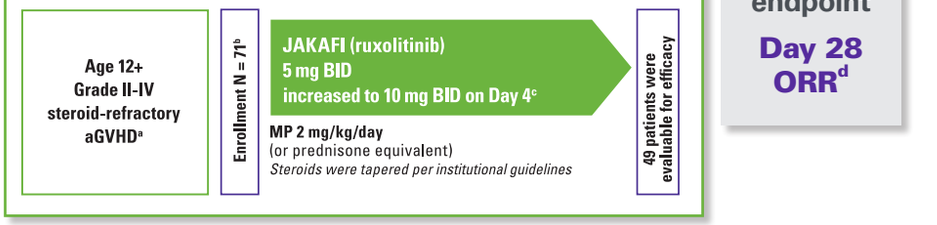
Please see related and other Important Safety Information on pages 6-7.

Please click here for Full Prescribing Information.

REACH1: An Open-Label, Single-Arm, Multicenter Study of Jakafi® (ruxolitinib) in Patients With Steroid-Refractory Acute GVHD[1]

FDA approval of Jakafi in steroid-refractory acute GVHD (aGVHD) was based on the REACH1 study[1]

REACH1: An Open-Label, Single-Arm, Multicenter Study[1,2]



aGVHD, acute graft-versus-host disease; BID, twice daily; CIBMTR, Center for International Blood and Marrow Transplant Research; MAGIC, Mount Sinai Acute GVHD International Consortium; MP, methylprednisolone; ORR, overall response rate; REACH, Ruxolitinib in PatiEnts With RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.

[a] Patients had Grade II to IV aGVHD defined according to the MAGIC criteria, occurring after allogeneic hematopoietic stem cell transplantation.[1]

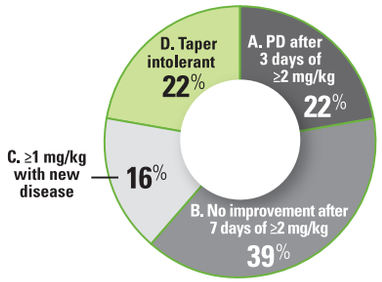
[b] Safety analysis based on all patients who received ruxolitinib (N = 71); 49 patients were eligible for efficacy analysis.[1]

[c] If hematologic parameters were stable and treatment-related toxicity was not observed.[1,3]

[d] Defined as the proportion of patients who had a complete response, partial response, or very good partial response at Day 28. GVHD responses were assessed based on the CIBMTR definitions.[1]

Patients Began Jakafi as Early as 3 Days After Steroid Initiation[3]

REACH1: Types of Patients With Steroid-Refractory aGVHD (N = 49), %[3]



A. Progression after 3 days of ≥2 mg/kg/day of methylprednisolone or equivalent

B. Failure to improve after 7 days of ≥2 mg/kg/day of methylprednisolone or equivalent

C. Treatment with ≥1 mg/kg/day of methylprednisolone for skin GVHD (or skin plus upper GI GVHD) and development of disease in an additional organ

D. Inability to achieve a 50% taper of steroid dose without a return of GVHD

aGVHD, acute graft-versus-host disease; GI, gastrointestinal; PD, progressive disease.

Patient Characteristics at Baseline (N = 49)[1,3]

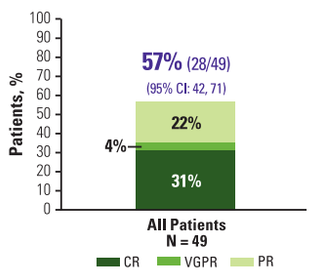
- 73% had Grade III or IV aGVHD
- 84% had visceral disease, and 55% had multiorgan involvement

Risk for Thrombocytopenia, Anemia, and Neutropenia

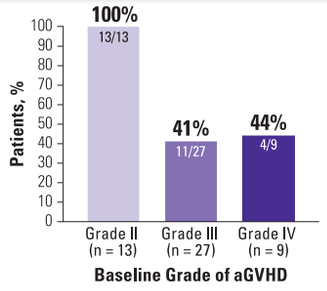
- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery

Day 28 Responses Were Achieved in the Majority of Patients Treated With Jakafi® (ruxolitinib) and Seen Across Grades[1]

Primary Endpoint: ORR at Day 28[1,a]



Subgroup Analysis: ORR at Day 28 by Baseline aGVHD Grade[1]



aGVHD, acute graft-versus-host disease; CR, complete response; ORR, overall response rate; PR, partial response; REACH, Ruxolitinib in PatiEnts With RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation; VGPR, very good partial response.

[a] In the REACH1 trial, ORR was defined as a complete response, very good partial response, or partial response by the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria.

Over half of Day 28 responders (54%; 15/28) achieved a CR

Day 28 responses seen in all 13 patients with Grade II aGVHD

Additional Response Data

For Day 28 Responders[3]

Median time to first response[a] was 7 days

68% responded by Day 7 visit[b]

86% responded by Day 14 visit

[a] Time from date of first Jakafi dosing to date when aGVHD response (CR, VGPR, or PR) was first reported, prior to initiation of new anti-aGVHD therapy.[3]

[b] A ±2-day window was permitted for assessment of response; thus, the "Day 7" visit included patients assessed up to Day 9.[3]

aGVHD, acute graft-versus-host disease.

Risk of Infection

- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

Please see related and other Important Safety Information on pages 6-7.
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Jakafi® ruxolitinib (tablets)

Jakafi® (ruxolitinib) Is an Oral Tablet That Allows for Individualized Dosing[1]

1 START

- Recommended starting dose: 5 mg orally BID
- Evaluate blood parameters before and during treatment with Jakafi
- Consider increasing dose to 10 mg BID after ≥3 days of treatment if ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing

2 MONITOR

- Dose reductions should be considered for platelet counts, ANCs, or bilirubin elevation, as described in the Full Prescribing Information

3 OPTIMIZE

- Doses may be modified based on safety and efficacy; doses of 5 mg QD to 10 mg BID may be given
  - Dose reductions may be used to manage side effects: 10 mg BID may be reduced to 5 mg BID; 5 mg BID may be reduced to 5 mg QD
- Patients who are unable to tolerate Jakafi at 5 mg QD should have treatment interrupted until their clinical and/or laboratory parameters recover
- Tapering may be considered after 6 months of treatment as clinically indicated in patients who have discontinued therapeutic doses of steroids
  - Taper Jakafi by 1 dose level approximately every 8 weeks (10 mg BID to 5 mg BID to 5 mg QD)
  - If aGVHD signs or symptoms recur during or after the taper of Jakafi, consider retreatment

See Full Prescribing Information for further details on dose modifications and use in special populations.

ANC, absolute neutrophil count; BID, twice daily; QD, once daily.

Other Important Safety Considerations

- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections and edema
- Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

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Safety Results for Jakafi® (ruxolitinib)

Nonhematologic Adverse Reactions Occurring in ≥15% of Patients[1,a]

Adverse Reactions	Jakafi (N = 71)	
	All Grades,[b] %	Grade 3-4, %
Infections[c]	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections[d]	32	28
Dyspnea	32	7
Viral infections[d]	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
Dizziness	16	0

CMV, cytomegalovirus; MedDRA, Medical Dictionary for Regulatory Activities.
[a] As of the 3-month data cutoff.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
[c] The infections category included any MedDRA terms that were site- or organ-specific (eg, urinary tract, lung).
[d] These categories included any infections that were attributed to a particular organism, regardless of site of infection (eg, *Clostridium difficile*, CMV, BK virus).

- In addition to Jakafi, patients in REACH1 received steroids ± other immunosuppressive medications[1,3]
- There were no fatal adverse reactions to Jakafi[1]
- Adverse reactions resulting in treatment discontinuation occurred in 31% of patients[1]
  - The most common adverse reaction leading to treatment discontinuation was infection (10%)

REACH, Ruxolitinib in PatiEnts With RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.

Selected Laboratory Abnormalities Worsening From Baseline[1]

Laboratory Parameter	Worst Grade During Treatment, %[a,b]	
	All Grades, %	Grade 3-4
Hematology		
Anemia	75	45
Thrombocytopenia	75	61
Neutropenia	58	40
Chemistry		
Elevated ALT	48	8
Elevated AST	48	6
Hypertriglyceridemia	11	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] As of the 3-month data cutoff.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

- Discontinuations due to treatment-emergent cytopenia were seen in 3% (2/71) of patients[3]

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- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
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- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections and edema
- Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

Please click here for Full Prescribing Information.

Jakafi® ruxolitinib (tablets)

Jakafi® (ruxolitinib) Is the First FDA-Approved Treatment for Patients 12 and Older With Steroid-Refractory Acute GVHD[1]

REACH1 was an open-label, single-arm, multicenter study in patients with Grade II-IV steroid-refractory aGVHD[1]

Majority of patients responded[1]

- 57% (28/49) overall response rate at Day 28 (complete response, very good partial response, or partial response)
- Over half of Day 28 responders (54%; 15/28) achieved a complete response
- Day 28 responses seen in all 13 patients with Grade II aGVHD

Median time to first response among Day 28 responders was 7 days[3]

- The majority of Day 28 responders (86%) responded by their Day 14 visit[3]

aGVHD, acute graft-versus-host disease; FDA, Food and Drug Administration; REACH, Ruxolitinib in PatiEnts With RefrACtory Graft-Versus-Host Disease After Allogeneic Stem Cell Transplantation.

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References: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Jagasia M, Perales M-A, Schroeder MA, et al. Results from REACH1, a single-cohort phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute graft-vs-host disease. Presented at: 60th American Society of Hematology (ASH) Annual Meeting and Exposition; December 1-4, 2018; San Diego, CA. Abstract 601. **3.** Data on file. Incyte Corporation. Wilmington, DE.

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