Jaypirca®
pirtobrutinib 50, 100 mg tablets

DOSING AND ADMINISTRATION GUIDE

Indications

- Jaypirca is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory (R/R) **mantle cell lymphoma (MCL)** after at least two lines of systemic therapy, including a BTK inhibitor.
- Jaypirca is also indicated for the treatment of adult patients with **chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL)** who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

  These indications are approved under accelerated approval based on response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

BCL-2=B-cell lymphoma 2; BTK=Bruton's tyrosine kinase.

Select Important Safety Information

Infections: Fatal and serious infections (bacterial, viral, fungal) and opportunistic infections (including *Pneumocystis jirovecii* pneumonia and fungal infection) have occurred in Jaypirca-treated patients. In a clinical trial of 593 patients with hematologic malignancies, Grade ≥3 infections occurred (24%), most commonly pneumonia (14%); fatal infections (4.4%), sepsis (6%), and febrile neutropenia (4%) occurred. In patients with CLL/SLL, Grade ≥3 infections occurred (32%), with fatal infections in 8%. Consider prophylaxis in patients at increased risk. Monitor patients for signs and symptoms of infection; based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Please see Important Safety Information on pages 4-6 and full Prescribing Information for Jaypirca.

One dose. One time a day.[1]

One more reason to explore Jaypirca.

A once-daily oral dose[1]

100 mg 100 mg

Recommended dose is 200 mg once daily[1]

May be taken **with or without food**[1]*

May be taken with **gastric acid-reducing agents**[1†]

May be taken **with select anticoagulants**[2]

- In a clinical trial, Jaypirca was allowed to be co-administered with anticoagulants except warfarin and vitamin K antagonists, which were not permitted[2]

- Two 100-mg tablets taken at the same time each day until disease progression or unacceptable toxicity[1]
  - Jaypirca is also available in 50-mg tablets for use when dose reductions are needed[1]
- Instruct patients to swallow tablets whole with water—do not crush, cut, or chew[1]
- If patients miss a dose by more than 12 hours, they should wait to take their next dose the following day, as scheduled[1]

Major hemorrhage occurred in patients taking Jaypirca with and without antithrombotic agents. Consider the risk/benefit of co-administering antithrombotic agents with Jaypirca and of withholding Jaypirca 3-7 days pre- and post-surgery. Monitor for signs of bleeding and reduce dose, temporarily withhold, or permanently discontinue Jaypirca, based on severity.[1]

*Can be taken with a high-fat meal.[1]

†No clinically significant differences in pirtobrutinib pharmacokinetics were observed when co-administered with omeprazole, a proton pump inhibitor.[1]

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Recommended Jaypirca dosage modifications for adverse reactions (ARs)[1]

Dose modifications can help manage select ARs[1]

START AT APPROVED DOSE (200 mg)

1st Occurrence	2nd Occurrence	3rd Occurrence	4th Occurrence
Interrupt until recovery to grade 1 or baseline	Interrupt until recovery to grade 1 or baseline	Interrupt until recovery to grade 1 or baseline	
RESTART at original dose **200 mg once daily***	**RESTART** at **100 mg once daily**	**RESTART** at **50 mg once daily**	**DISCONTINUE**

Adverse Reactions

- Grade 3 or greater nonhematologic toxicity*
- Absolute neutrophil count <1 to 0.5 x 10^9/L with fever and/or infection
- Absolute neutrophil count <0.5 x 10^9/L lasting ≥7 days
- Platelet count <50 to 25 x 10^9/L with bleeding
- Platelet count <25 x 10^9/L

*Evaluate benefit-risk before resuming treatment at the same dose for a Grade 4 non-hematological toxicity.[1]

Dose modification is not recommended for asymptomatic lymphocytosis. Asymptomatic lipase increase may not necessarily warrant dose modification.[1]

For patients with severe renal impairment (eGFR 15-29 mL/min), reduce Jaypirca dose to 100 mg if the current dose is 200 mg once daily; otherwise reduce dose by 50 mg. If the current dose is 50 mg once daily, discontinue Jaypirca. No dose adjustment recommended in patients with mild to moderate renal impairment (eGFR 30-89 mL/min).[1]

Avoid concomitant use of strong CYP3A inhibitors with Jaypirca. If concomitant use is unavoidable, reduce the Jaypirca dose by 50 mg. If the current dosage is 50 mg once daily, interrupt Jaypirca treatment for the duration of strong CYP3A inhibitor use. After discontinuation of a strong CYP3A inhibitor for 5 half-lives, resume the Jaypirca dose that was taken prior to initiating the strong CYP3A inhibitor.[1]

Avoid concomitant use of strong or moderate CYP3A inducers with Jaypirca. If concomitant use with moderate CYP3A inducers is unavoidable and the current dose of Jaypirca is 200 mg once daily, increase the dose to 300 mg. If the current dosage is 50 mg or 100 mg once daily, increase the dose by 50 mg.[1]

eGFR=estimated glomerular filtration rate.

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Important Safety Information for Jaypirca (pirtobrutinib)

Infections: Fatal and serious infections (including bacterial, viral, fungal) and opportunistic infections occurred in Jaypirca-treated patients. In a clinical trial, Grade ≥3 infections occurred in 24% of patients with hematologic malignancies, most commonly pneumonia (14%); fatal infections occurred (4.4%). Sepsis (6%) and febrile neutropenia (4%) occurred. In patients with CLL/SLL, Grade ≥3 infections occurred (32%), with fatal infections occurring in 8%. Opportunistic infections included *Pneumocystis jirovecii* pneumonia and fungal infection. Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients at increased risk for infection, including opportunistic infections. Monitor patients for signs and symptoms, evaluate promptly, and treat appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Hemorrhage: Fatal and serious hemorrhage has occurred with Jaypirca. Major hemorrhage (Grade ≥3 bleeding or any central nervous system bleeding) occurred in 3% of patients, including gastrointestinal hemorrhage; fatal hemorrhage occurred (0.3%). Bleeding of any grade, excluding bruising and petechiae, occurred (17%). Major hemorrhage occurred in patients taking Jaypirca with (0.7%) and without (2.3%) antithrombotic agents. Consider risks/benefits of co-administering antithrombotic agents with Jaypirca. Monitor patients for signs of bleeding. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca. Consider benefit/risk of withholding Jaypirca 3-7 days pre- and post-surgery depending on type of surgery and bleeding risk.

Cytopenias: Jaypirca can cause cytopenias, including neutropenia, thrombocytopenia, and anemia. In a clinical trial, Grade 3 or 4 cytopenias, including decreased neutrophils (26%), decreased platelets (12%), and decreased hemoglobin (12%), developed in Jaypirca-treated patients. Grade 4 decreased neutrophils (14%) and Grade 4 decreased platelets (6%) developed. Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Cardiac Arrhythmias: Cardiac arrhythmias occurred in patients who received Jaypirca. In a clinical trial of patients with hematologic malignancies, atrial fibrillation or flutter were reported in 3.2% of Jaypirca-treated patients, with Grade 3 or 4 atrial fibrillation or flutter in 1.5%. Other serious cardiac arrhythmias such as supraventricular tachycardia and cardiac arrest occurred (0.5%). Patients with cardiac risk factors such as hypertension or previous arrhythmias may be at increased risk. Monitor for signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea) and manage appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Second Primary Malignancies: Second primary malignancies, including non-skin carcinomas, developed in 9% of Jaypirca-treated patients. The most frequent malignancy was non-melanoma skin cancer (4.6%). Other second primary malignancies included solid tumors (including genitourinary and breast cancers) and melanoma. Advise patients to use sun protection and monitor for development of second primary malignancies.

Hepatotoxicity, Including Drug-Induced Liver Injury (DILI): Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of DILI, has occurred in patients treated with BTK inhibitors, including Jaypirca. Evaluate bilirubin and transaminases at baseline and throughout Jaypirca treatment. For patients who develop abnormal liver tests after Jaypirca, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold Jaypirca. Upon confirmation of DILI, discontinue Jaypirca.

Please see Important Safety Information continued on next page and full Prescribing Information and Patient Information for Jaypirca.

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Important Safety Information for Jaypirca (pirtobrutinib) (cont'd)

Embryo-Fetal Toxicity: Jaypirca can cause fetal harm in pregnant women. Administration of pirtobrutinib to pregnant rats caused embryo-fetal toxicity, including embryo-fetal mortality and malformations at maternal exposures (AUC) approximately 3-times the recommended 200 mg/day dose. Advise pregnant women of potential fetal risk and females of reproductive potential to use effective contraception during treatment and for one week after last dose.

Adverse Reactions (ARs) in Patients Who Received Jaypirca

The most common (≥20%) ARs in the BRUIN pooled safety population of patients with hematologic malignancies (n=593) were decreased neutrophil count (46%), decreased hemoglobin (39%), fatigue (32%), decreased lymphocyte count (31%), musculoskeletal pain (30%), decreased platelet count (29%), diarrhea (24%), COVID-19 (22%), bruising (21%), cough (20%).

Mantle Cell Lymphoma

Serious ARs occurred in 38% of patients. Serious ARs occurring in ≥2% of patients were pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). **Fatal ARs** within 28 days of last Jaypirca dose occurred in 7% of patients, most commonly due to infections (4.7%), including COVID-19 (3.1% of all patients).

Dose Modifications and Discontinuations: ARs led to dose reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dosage modification in >5% of patients included pneumonia and neutropenia. ARs resulting in permanent discontinuation in >1% of patients included pneumonia.

Most common ARs (≥15%), excluding laboratory terms (all Grades %; Grade 3-4 %): fatigue (29; 1.6), musculoskeletal pain (27; 3.9), diarrhea (19; -), edema (18; 0.8), dyspnea (17; 2.3), pneumonia (16; 14), bruising (16; -).

Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in ≥10% of Patients: hemoglobin decreased (42; 9), platelet count decreased (39; 14), neutrophil count decreased (36; 16), lymphocyte count decreased (32; 15), creatinine increased (30; 1.6), calcium decreased (19; 1.6), AST increased (17; 1.6), potassium decreased (13; 1.6), sodium decreased (13; -), lipase increased (12; 4.4), alkaline phosphatase increased (11; -), ALT increased (11; 1.6), potassium increased (11; 0.8). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (10), platelets decreased (7), lymphocytes decreased (6).

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Serious ARs occurred in 56% of patients. Serious ARs occurring in ≥5% of patients were pneumonia (18%), COVID-19 (9%), sepsis (7%), and febrile neutropenia (7%). **Fatal ARs** within 28 days of last Jaypirca dose occurred in 11% of patients, most commonly due to infections (10%), including sepsis (5%) and COVID-19 (2.7%).

Dose Modifications and Discontinuations: ARs led to dose reductions in 3.6%, treatment interruption in 42%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dose reductions in >1% included neutropenia; treatment interruptions in >5% of patients included pneumonia, neutropenia, febrile neutropenia, and COVID-19; permanent discontinuation in >1% of patients included second primary malignancy, COVID-19, and sepsis.

Please see Important Safety Information continued on next page and full Prescribing Information and Patient Information for Jaypirca.

Important Safety Information for Jaypirca (pirtobrutinib) (cont'd)

Most common ARs (≥20%), excluding laboratory terms (all Grades %; Grade 3-4 %): fatigue (36; 2.7), bruising (36; -), cough (33; -), musculoskeletal pain (32; 0.9), COVID-19 (28; 7), pneumonia (27; 16), diarrhea (26; -), abdominal pain (25; 2.7), dyspnea (22; 2.7), hemorrhage (22; 2.7), edema (21; -), nausea (21; -), pyrexia (20; 2.7), headache (20; 0.9).

Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in ≥20% of Patients: neutrophil count decreased (63; 45), hemoglobin decreased (48; 19), calcium decreased (40; 2.8), platelet count decreased (30; 15), sodium decreased (30; -), lymphocyte count decreased (23; 8), ALT increased (23; 2.8), AST increased (23; 1.9), creatinine increased (23; -), lipase increased (21; 7), alkaline phosphatase increased (21; -). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (23).

Drug Interactions

Strong CYP3A Inhibitors: Concomitant use with Jaypirca increased pirtobrutinib systemic exposure, which may increase risk of Jaypirca ARs. Avoid use of strong CYP3A inhibitors with Jaypirca. If concomitant use is unavoidable, reduce Jaypirca dosage according to approved labeling.

Strong or Moderate CYP3A Inducers: Concomitant use with Jaypirca decreased pirtobrutinib systemic exposure, which may reduce Jaypirca efficacy. Avoid concomitant use of Jaypirca with strong or moderate CYP3A inducers. If concomitant use with moderate CYP3A inducers is unavoidable, increase Jaypirca dosage according to approved labeling.

Sensitive CYP2C8, CYP2C19, CYP3A, P-gp, or BCRP Substrates: Concomitant use with Jaypirca increased their plasma concentrations, which may increase risk of adverse reactions related to these substrates for drugs that are sensitive to minimal concentration changes. Follow recommendations for these sensitive substrates in their approved labeling.

Use in Special Populations

Pregnancy and Lactation: Due to potential for Jaypirca to cause fetal harm, verify pregnancy status in females of reproductive potential prior to starting Jaypirca and advise use of effective contraception during treatment and for one week after last dose. Presence of pirtobrutinib in human milk is unknown. Advise women not to breastfeed while taking Jaypirca and for one week after last dose.

Geriatric Use: In the pooled safety population of patients with hematologic malignancies, patients aged ≥65 years experienced higher rates of Grade ≥3 ARs and serious ARs compared to patients <65 years of age.

Renal Impairment: Severe renal impairment increases pirtobrutinib exposure. Reduce Jaypirca dosage in patients with severe renal impairment according to approved labeling.

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Notes

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References: 1. Jaypirca. Prescribing Information. Lilly USA, LLC. **2.** Data on File, Lilly USA, LLC, DOF-PT-US-0009.