RxAdvance

# NEW DRUG APPROVAL

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|---|---|
| **Brand Name** | Jaypirca™ |
| **Generic Name** | pirtobrutinib |
| **Drug Manufacturer** | Loxo Oncology; Eli Lilly |

## New Drug Approval

FDA Approval Date: January 27, 2023

Review Designation: Priority; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 216059

Dispensing restriction: N/A

## Place in Therapy

### DISEASE DESCRIPTION & EPIDEMIOLOGY

Mantle cell lymphoma (MCL) is a rare type of B cell non-Hodgkin lymphoma (NHL). NHL is a cancer of the lymphatic system. Mantle cell lymphoma affects the B cells. It develops in the part of the lymph node called the mantle zone. The abnormal B lymphocytes start to collect in the lymph nodes or body organs. They can then form tumours and begin to cause problems within the lymphatic system or the organ where they are growing.

Mantle cell lymphoma is mature B-cell non-Hodgkin lymphoma that represents 3%–10% of all non-Hodgkin lymphomas in the United States. The incidence of MCL is approximately 4–8 cases per million persons per year. The incidence increases with age, with about three-quarters of patients being male and Caucasian. The median age at diagnosis is 68 years. By the time it is diagnosed, MCL has usually spread to the lymph nodes, bone marrow, and other organs. MCL usually responds well to first-line therapy; however, most patients develop recurring disease. In relapsed lymphoma, the disease reappears or grows again after a period of remission, while in refractory lymphoma, the disease does not respond to treatment or responds only briefly.

## Efficacy

**Mantle Cell Lymphoma**

The efficacy of Jaypirca™ in patients with MCL was evaluated in BRUIN [NCT03740529], an open-label, international, single-arm study of Jaypirca™ as monotherapy. Efficacy was based on 120 patients with MCL treated with Jaypirca™ who were previously treated with a BTK inhibitor. Jaypirca™ was given orally at a dose of 200 mg once daily and was continued until disease progression or unacceptable toxicity. Patients with active central nervous system lymphoma or allogeneic hematopoietic stem cell transplantation (HSCT) or CAR-T cell therapy within 60 days were excluded.

The median age was 71 years (range: 46 to 88 years); 79% were male; 78% were White, 14% Asian, 1.7% Black or African American. Seventy-eight percent of patients had the classic/leukemic variant of MCL, 12% had pleomorphic MCL, and 11% had blastoid MCL. The simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) score was low in 15%, intermediate in 59%, and high in 26% of patients. Patients received a median number of 3 prior lines of therapy (range: 1 to 9) with 93% having received 2 or more prior lines. All received 1 or more prior lines of therapy containing a BTK inhibitor; other prior therapies included chemoimmunotherapy in 88%, HSCT in 20%, lenalidomide in 18%, and CAR-T therapy in 9%. The most common prior BTK inhibitors received were ibrutinib (67%), acalabrutinib (30%), and zanubrutinib (8%). Patients may have received more than one prior

BTK inhibitor; 83% of patients discontinued the last BTK inhibitor for refractory or progressive disease, 10% discontinued for toxicity, and 5% discontinued for other reasons.

Efficacy was based on overall response rate (ORR) and duration of response (DOR), as assessed by an independent review committee (IRC) using 2014 Lugano criteria. Efficacy results are shown in Table 1. Additionally, the Kaplan-Meier estimate for the DOR rate at 6 months was 65.3% (95% CI: 49.8, 77.1).

**Table 1: Efficacy Results per IRC in Patients with MCL Previously Treated with a BTK Inhibitor**

| Outcome | Jaypirca™ 200 mg once daily (N = 120) |
|---|---|
| **Overall Response Rate** [a,b] | |
| ORR, n | 60 (50%) |
| (95% CI, %) | 41, 59 |
| CR, n | 15 (13%) |
| PR, n | 45 (38%) |
| **Time to Response** | |
| Median (range), months | 1.8 (0.8, 4.2) |
| **Duration of Response** [c] | |
| Number censored, n | 36 |
| Median DOR, months (95% CI) | 8.3 (5.7, NE) |

CI, confidence interval; CR, complete response; DOR, duration of response; PR, partial response; NE, not estimable.
[a] PET-CT scans were utilized in response assessments (in 41% of patients), with the remainder being assessed by CT scans only.
[b] ORR using CT scan-based assessments in all patients was 48% (95% CI: 38, 57) and CR rate was 13%.
[c] Based on Kaplan-Meier estimation. Estimated median follow-up was 7.3 months.

## Safety

### ADVERSE EVENTS

In the BRUIN study, Jaypirca™ is used as a single-agent, administered at 200 mg once daily in 583 patients with hematologic malignancies. Among these 583 patients, the median duration of exposure was 7.5 months, 56% were exposed for at least 6 months and 29% were exposed for at least one year. In this pooled safety population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were decreased neutrophil count (41%), decreased hemoglobin (37%), decreased platelet count (27%), fatigue (27%), musculoskeletal pain (26%), decreased lymphocyte count (24%), bruising (20%), and diarrhea (20%).

Serious adverse reactions occurred in 38% of patients who received Jaypirca™. Serious adverse reactions that occurred 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 adverse reactions within 28 days of the last dose of JAYPIRCA occurred in 7% of patients, most commonly due to infections (4.7%) including COVID-19 (3.1% of all patients).

Adverse reactions led to dosage reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of JAYPIRCA in 9%. Adverse reactions that resulted in dosage modification in > 5% of patients included pneumonia and neutropenia. Adverse reactions which resulted in permanent discontinuation of JAYPIRCA in > 1% of patients included pneumonia.

The most common adverse reactions (≥ 15%), excluding laboratory terms, were fatigue, musculoskeletal pain, diarrhea, edema, dyspnea, pneumonia, and bruising.

| Table 2: Adverse Reactions (≥ 10%) in Patients with MCL Who Received Jaypirca™ | | |
|---|---|---|
| | Jaypirca™ 200 mg once daily | |
| | N = 128 | |
| **Adverse Reactions** [a] | **All Grades (%)** | **Grade 3-4 (%)** |
| **General Disorders** | | |
| Fatigue | 29 | 1.6 |
| Edema | 18 | 0.8 |
| Fever | 13 | - |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Musculoskeletal pain | 27 | 3.9 |
| Arthritis or arthralgia | 12 | 0.8 |
| **Gastrointestinal Disorders** | | |
| Diarrhea | 19 | - |
| Constipation | 13 | - |
| Abdominal pain | 11 | 0.8 |
| Nausea | 11 | - |
| **Respiratory, thoracic, and mediastinal disorders** | | |
| Dyspnea | 17 | 2.3 |
| Cough | 14 | - |
| **Injury** | | |
| Bruising | 16 | - |
| **Infections** | | |
| Pneumonia | 16 [b] | 14 |
| Upper respiratory tract infections | 10 | 0.8 |
| Nervous system disorders | | |
| Peripheral neuropathy | 14 | 0.8 |
| Dizziness | 10 | - |
| Skin and subcutaneous disorders | | |
| Rash | 14 | - |
| **Vascular disorders** | | |
| Hemorrhage | 11 [c] | 3.1 |

[a] Each term listed includes other related terms.
[b] includes 1 fatality from COVID-19 pneumonia

[c] includes 1 fatality from hemorrhage

Clinically relevant adverse reactions in < 10% include vision changes, memory changes, headache, urinary tract infection, herpesvirus infection, and tumor lysis syndrome.

## WARNINGS & PRECAUTIONS

**Infections**

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients treated with Jaypirca™. In the clinical trial, Grade 3 or higher infections occurred in 17% of 583 patients, most commonly pneumonia (9%), with fatal infections occurring in 4.1% of patients. Sepsis occurred in 4.5% of patients and febrile neutropenia in 2.9%. Opportunistic infections after treatment with Jaypirca™ have included, but are not limited to, Pneumocystis jirovecii pneumonia and fungal infection.

Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients who are at increased risk for infections, including opportunistic infections. Monitor patients for signs and symptoms of infection, 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 (defined as Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 2.4% of 583 patients treated with Jaypirca™, including gastrointestinal hemorrhage; fatal hemorrhage occurred in 0.2% of patients. Bleeding of any grade, excluding bruising and petechiae, occurred in 14% of patients.

Major hemorrhage occurred in 1.7% of patients taking Jaypirca™without antithrombotic agents and 0.7% of patients taking Jaypirca™ with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with Jaypirca™. Monitor patients for signs of bleeding. Based on severity of bleeding, reduce dose, temporarily withhold, or permanently discontinue Jaypirca™.

Consider the benefit-risk of withholding Jaypirca™ for 3 to 7 days pre- and post-surgery depending upon the type of surgery and risk of bleeding.

**Cytopenias**

Grade 3 or 4 cytopenias, including neutropenia (24%), anemia (11%), and thrombocytopenia (11%) have developed in patients treated with Jaypirca™. In the clinical trial, Grade 4 neutropenia developed in 13% of patients and Grade 4 thrombocytopenia developed in 5% of patients. Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca™.

**Atrial Fibrillation and Atrial Flutter**

Atrial fibrillation and atrial flutter were reported in recipients of Jaypirca™. Atrial fibrillation or flutter were reported in 2.7% of patients, with Grade 3 or 4 atrial fibrillation or flutter reported in 1.0% of 583 patients in the clinical trial. 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 6% of 583 patients treated with Jaypirca™ monotherapy. The most frequent malignancy was non-melanoma skin cancer, reported in 3.8% of 583 patients. Other second primary malignancies included solid tumors (including genitourinary and breast cancers)

and melanoma. Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

**Embryo-Fetal Toxicity**
Based on findings in animals, Jaypirca™ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of pirtobrutinib to pregnant rats during the period of organogenesis caused embryofetal toxicity including embryo-fetal mortality and malformations at maternal exposures (AUC) approximately 3-times the recommended dose of 200 mg once daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Jaypirca™ and for one week after the last dose.

### CONTRAINDICATIONS

None reported.

## Clinical Pharmacology

### MECHANISMS OF ACTION

Pirtobrutinib is a small molecule, noncovalent inhibitor of BTK. BTK is a signaling protein of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Pirtobrutinib binds to wild type BTK and BTK harboring C481 mutations, leading to inhibition of BTK kinase activity. In nonclinical studies, pirtobrutinib inhibited BTK-mediated B-cell CD69 expression and inhibited malignant B-cell proliferation. Pirtobrutinib showed dose-dependent anti-tumor activities in BTK wild type and BTK C481S mutant mouse xenograft models.

## Dose & Administration

### ADULTS

Recommended dosage: 200 mg orally once daily until disease progression or unacceptable toxicity. Manage toxicity using treatment interruption, dosage reduction, or discontinuation.

### PEDIATRICS

Safety and effectiveness of Jaypirca™ have not been established in pediatric patients.

### GERIATRICS

Refer to adult dosing.

### RENAL IMPAIRMENT

For patients with severe renal impairment (eGFR 15-29 mL/min), reduce the Jaypirca™ dose to 100 mg once daily if the current dose is 200 mg once daily otherwise reduce the dose by 50 mg. If the current dosage is 50 mg once daily discontinue Jaypirca™.

### HEPATIC IMPAIRMENT

None.

## Product Availability

### DOSAGE FORM(S) & STRENGTH(S)

Tablets: 50 mg, 100 mg