U.S. FDA approves expanded indication for Lilly's Jaypirca (pirtobrutinib), the first and only non-covalent (reversible) BTK inhibitor, for adults with relapsed or refractory CLL/SLL previously treated with a covalent BTK inhibitor

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Approval is based on results from the BRUIN CLL-321 trial, the only randomized Phase 3 study in CLL/SLL in which all patients were previously treated with a covalent BTK inhibitor

This expanded indication represents a substantial increase in the number of CLL/SLL patients who may benefit from Jaypirca and aligns with the patient population endorsed by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

INDIANAPOLIS, Dec. 3, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that the U.S. Food and Drug Administration (FDA) has granted approval to Jaypirca (pirtobrutinib, 100 mg & 50 mg tablets) for the treatment of adults with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have previously been treated with a covalent Bruton tyrosine kinase (BTK) inhibitor. This FDA action expands the Jaypirca label to include patients earlier in their treatment course and also converts the December 2023 accelerated approval for later-line CLL/SLL to a traditional approval.[1]

"Pirtobrutinib is the only medicine in CLL or SLL that has been prospectively studied in a randomized trial of patients previously treated with a covalent BTK inhibitor, and I am excited to see this expanded FDA approval recognize the benefit it can deliver to this broader group of patients," said Jeff Sharman, M.D., Disease Chair, Hematology Executive Committees, SCRI at Willamette Valley Cancer Institute and Research Center, and one of the principal investigators of the BRUIN CLL-321 trial. "When covalent BTK inhibitors are no longer an option due to disease progression or intolerance, pirtobrutinib enables physicians to extend the benefits of targeting the BTK pathway, offering continuity in the CLL or SLL treatment experience."

Jaypirca, the first and only FDA-approved non-covalent (reversible) BTK inhibitor, is a highly selective kinase inhibitor that utilizes a novel non-covalent binding mechanism to extend the benefit of targeting the BTK pathway in patients with relapsed or refractory CLL/SLL previously treated with a covalent BTK inhibitor (ibrutinib, acalabrutinib, or zanubrutinib).[1,2]

"This label expansion allows physicians to use Jaypirca directly after a covalent BTK inhibitor, the setting where we have always believed it has its most unique potential impact for patients," said Jacob Van Naarden, executive vice president and president of Lilly Oncology. "With robust efficacy and safety evidence from the only study of its kind in the post-covalent BTK inhibitor treatment setting, we're proud to now offer this therapy to more patients with CLL or SLL at an earlier stage of their treatment plan."

"For CLL or SLL patients who progress following treatment with an irreversible or covalently binding BTK inhibitor, having additional therapeutic options is critical," said Brian Koffman, M.D., co-founder and chief medical officer emeritus at CLL Society. "With this approval, physicians and patients can stay in the same broad class of medicines with a treatment that offers meaningful impact on patient outcomes, saving the potential to use medicines with different targets for later therapy."

Lilly is studying Jaypirca in CLL/SLL in multiple Phase 3 studies. Details on the trials can be found by visiting clinicaltrials.gov.

See Important Safety Information below and full Prescribing Information for additional information.

Click here to view the CLL infographic.

About BRUIN CLL-321
BRUIN CLL-321 is a Phase 3, randomized, open-label study of Jaypirca versus investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) in covalent Bruton tyrosine kinase (BTK) inhibitor pre-treated patients with relapsed and refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The trial enrolled 238 patients, who were randomized 1:1 to receive Jaypirca (200 mg orally, once daily) or investigator's choice of either IdelaR or BR per labeled doses. This trial's primary endpoint is progression-free survival (PFS) per 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria, as assessed by blinded independent review committee (IRC). Secondary endpoints include PFS, as assessed by investigator; overall response rate (ORR) and duration of response (DoR); event-free survival; overall survival (OS) and time to next treatment (TTNT); safety and tolerability; and patient-reported outcomes (PRO).

About Jaypirca (pirtobrutinib)
Jaypirca (pirtobrutinib, formerly known as LOXO-305) (pronounced jay-pihr-kaa) is a highly selective (300 times more selective for BTK versus 98% of other kinases tested in preclinical studies), non-covalent (reversible) inhibitor of the enzyme BTK.[2] BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL).[3,4] Jaypirca is a U.S. FDA-approved oral prescription medicine, 100 mg or 50 mg tablets taken as a once-daily 200 mg dose with or without food until disease progression or unacceptable toxicity.

About Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of slow-growing non-Hodgkin lymphoma that develop from white blood cells known as lymphocytes.[5] CLL is one of the most common types of leukemia in adults.[5] In the U.S., CLL accounts for about one-quarter of the new cases of leukemia and there will be approximately 23,690 new cases of CLL diagnosed this year.[5,6] SLL is identical to CLL

from a pathologic and immunophenotypic standpoint, with the main difference between them being the location of the cancer cells.[5] In CLL, the cancer cells are present in the blood, and in SLL, the cancer cells are found in the lymph nodes.[5]

INDICATIONS FOR JAYPIRCA (pirtobrutinib)
Jaypirca is indicated for the treatment of

- Adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have previously been treated with a covalent BTK inhibitor.
- Adult patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical trial benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION FOR JAYPIRCA (pirtobrutinib)

Infections: Fatal and serious infections (including bacterial, viral, fungal) and opportunistic infections occurred in Jaypirca-treated patients. Across clinical trials, Grade ≥3 infections occurred (25%), most commonly pneumonia (20%); fatal infections (5%), sepsis (6%), and febrile neutropenia (3.8%) 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 for signs and symptoms, evaluate, and treat. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Hemorrhage: Fatal and serious hemorrhage has occurred with Jaypirca. Across clinical trials, major hemorrhage (Grade ≥3 bleeding or any central nervous system bleeding) occurred (2.6%), including gastrointestinal hemorrhage; fatal hemorrhage occurred (0.3%). Bleeding of any grade, excluding bruising and petechiae, occurred (16%). Major hemorrhage occurred when taking Jaypirca with (2.0%) and without (0.6%) antithrombotic agents. Consider risks/benefits of co-administering antithrombotic agents with Jaypirca. Monitor for signs of bleeding. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca. Consider withholding Jaypirca 3-7 days pre- and post-surgery based on surgery type and bleeding risk.

Cytopenias: Jaypirca can cause cytopenias, including neutropenia, thrombocytopenia, and anemia. Across clinical trials, Grade 3 or 4 cytopenias, including decreased neutrophils (27%), decreased platelets (13%), and decreased hemoglobin (11%), developed. Grade 4 decreased neutrophils (15%) and Grade 4 decreased platelets (6%) developed. Monitor complete blood counts regularly. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Cardiac Arrhythmias: Cardiac arrhythmias occurred in patients taking Jaypirca. Across clinical trials, atrial fibrillation or flutter were reported in 3.4% of Jaypirca treated patients, with Grade 3 or 4 atrial fibrillation or flutter in 1.6%. Other serious cardiac arrhythmias such as supraventricular tachycardia and cardiac arrest occurred (0.4%). Cardiac risk factors such as hypertension or previous arrhythmias may increase risk. Monitor and manage signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea). Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Second Primary Malignancies: Across clinical trials, second primary malignancies, including non-skin carcinomas, developed in 9% of Jaypirca-treated patients, most frequently non-melanoma skin cancer (4.4%). 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. If DILI is confirmed, discontinue Jaypirca.

Embryo-Fetal Toxicity: Jaypirca can cause fetal harm. 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 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 (≥30%) ARs in the pooled safety population of patients with hematologic malignancies (n=704) were decreased neutrophil count (54%), decreased hemoglobin (43%), decreased leukocytes (32%), fatigue (31%), decreased platelets (31%), decreased lymphocyte count (31%), calcium decreased (30%).

Mantle Cell Lymphoma

Serious ARs occurred in 38% of patients, with pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%) occurring in ≥2% of patients. **Fatal ARs** within 28 days of last 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 Due to ARs: Dose reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of Jaypirca in 9% of patients. Permanent discontinuation in >1% of patients included pneumonia.

Most common ARs (≥15%) and Select Laboratory Abnormalities (≥10%) (all Grades %; Grade 3-4 %): hemoglobin decreased (42; 9), platelet count decreased (39; 14), neutrophil count decreased (36; 16), lymphocyte count decreased (32; 15), creatinine increased (30; 1.6), fatigue (29; 1.6), musculoskeletal pain (27; 3.9), calcium decreased (19; 1.6), diarrhea (19; -), edema (18; 0.8), dyspnea (17; 2.3), AST increased (17; 1.6), pneumonia (16; 14), bruising (16; -), potassium decreased (13; 1.6), sodium decreased (13; -), lipase increased (12; 4.4), ALT increased (11; 1.6), potassium increased (11; 0.8), alkaline phosphatase increased (11; -). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (10), platelets decreased (7), lymphocytes decreased (6).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma from Single-Arm and Randomized Controlled Clinical Trials

Serious ARs occurred in 47-56% of patients across clinical trials. Serious ARs in ≥5% of patients in the single-arm trial were pneumonia (18%), COVID-19 (9%), sepsis (7%), febrile neutropenia (7%). Serious ARs in ≥3% of patients in the randomized controlled trial were pneumonia (21%), COVID-19 (5%), sepsis (3.4%). **Fatal ARs** within 28-30 days of last Jaypirca dose occurred in 8-11% of patients, most commonly due to infections (7-10%), including sepsis (5%), COVID-19 (2.7-5%), and pneumonia (3.4%).

Dose Modifications and Discontinuations Due to ARs: Dose reductions in 3.6-10%, treatment interruption in 42-51%, and permanent discontinuation of Jaypirca in 9-17% of patients. Permanent discontinuation in >1% of patients included second primary malignancy, pneumonia, COVID-19, neutropenia, sepsis, anemia, and cardiac arrythmias.

Most common ARs and Select Laboratory Abnormalities (≥20%) (all Grades %, Grade 3-4 %)--in a randomized controlled trial: neutrophil count decreased (54; 26), hemoglobin decreased (45; 10), platelet count decreased (37; 17), pneumonia (28; 16), ALT increased (25; 1.8), creatinine increased (25; -), calcium decreased (23; 0.9), sodium decreased (22; 0.9), bilirubin increased (21; 0.9), upper respiratory tract infections (21; 0.9); **in a single-arm trial:** neutrophil count decreased (63; 45), hemoglobin decreased (48; 19), calcium decreased (40; 2.8), fatigue (36; 2.7), bruising (36; -), cough (33; -), musculoskeletal pain (32; 0.9), platelet count decreased (30; 15), sodium decreased (30; -), COVID-19 (28; 7), pneumonia (27; 16), diarrhea (26; -), abdominal pain (25; 2.7), lymphocyte count decreased (23; 8), ALT increased (23; 2.8), AST increased (23; 1.9), creatinine increased (23; -), dyspnea (22; 2.7), hemorrhage (22; 2.7), lipase increased (21; 7), alkaline phosphatase increased (21; -), edema (21; -), nausea (21; -), pyrexia (20; 2.7), headache (20; 0.9). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (23).

Drug Interactions

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

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

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

Use in Specific 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. Presence of pirtobrutinib in human milk is unknown. Advise women to use effective contraception and to not 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: Because severe renal impairment increases pirtobrutinib exposure, reduce Jaypirca dose in these patients according to approved labeling.

PT HCP ISI MCL_CLL Q42025

Please see Prescribing Information and Patient Information for Jaypirca.

About Lilly
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Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Jaypirca as a treatment for adults with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have been previously treated with a covalent BTK inhibitor and as a treatment for adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor, and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical

product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, or that Jaypirca will receive additional regulatory approvals. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

Endnotes & References

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