▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

# AUSTRALIAN PRODUCT INFORMATION – JAYPIRCA® (PIRTOBRUTINIB) FILM-COATED TABLETS

## 1 NAME OF THE MEDICINE

Pirtobrutinib

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

**JAYPIRCA pirtobrutinib 50 mg film-coated tablet**

Each film coated tablet contains 50 mg of pirtobrutinib.

Excipients with known effect

Each film coated tablet contains 38 mg of lactose (as monohydrate).

**JAYPIRCA pirtobrutinib 100 mg film-coated tablet**

Each film coated tablet contains 100 mg of pirtobrutinib.

Excipients with known effect

Each film coated tablet contains 77 mg of lactose (as monohydrate).

For the full list of excipients, see section **6.1 List of excipients.**

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

JAYPIRCA 50 mg film-coated tablets

Blue, approx. 9 x 9 mm arc triangle shaped tablet debossed with “Lilly 50” on one side and “6902” on the other side.

JAYPIRCA 100 mg film coated tablets

Blue, approx. 10 mm round tablet debossed with “Lilly 100” on one side and “7026” on the other side.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC INDICATIONS

### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

JAYPIRCA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who have been previously treated with a covalent Bruton's tyrosine kinase (BTK) inhibitor.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with JAYPIRCA should be initiated and supervised by physicians experienced in the use of anticancer therapies.

### Dosage

The recommended dose is 200 mg once daily.

Treatment should be continued until disease progression or unacceptable toxicity.

### Dose Modification for Adverse Reactions

JAYPIRCA dosing should be interrupted until recovery to Grade 1 or baseline when the patient experiences the following event:

- Grade 3 neutropenia with fever and/or infection
- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia
- Grade 3 or 4 non-haematologic toxicity

**Table 1 Recommended dose modifications for adverse reactions**

| **Occurrences requiring dose modifications** | **Dose modification[a]** |
|---|---|
| **First occurrence** | Resume at original dosage of 200 mg once daily. |
| **Second occurrence** | Resume at reduced dose of 100 mg once daily. |
| **Third occurrence** | Resume at reduced dose of 50 mg once daily. |
| **Fourth occurrence** | Discontinue JAYPIRCA. |

[a] Dose modification is not recommended for asymptomatic lymphocytosis or asymptomatic lipase increase.

Missed Dose

If more than 12 hours have passed after a patient has missed a dose, instruct the patient to take the next dose at its scheduled time; an additional dose should not be taken.

**Method of administration**

JAYPIRCA is for oral use. Do not split, crush or chew the tablet.

JAYPIRCA may be taken with or without food.

Patients should take the dose at approximately the same time every day.

Instruct patients that if vomiting occurs, do not take an additional dose; continue with the next scheduled dose.

**Special populations**

Renal impairment

No dose adjustment is required for patients with mild, or moderate 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.

There are no data in patients on dialysis (see section **5.2 Pharmacokinetic properties**).

Hepatic impairment

No dose adjustment is required for patients with mild, moderate, or severe hepatic impairment (see section **5.2 Pharmacokinetic properties**).

Interactions requiring dose adjustments

*Moderate and strong CYP3A inducers*

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, consider increasing the dose to 300 mg once daily. If the current dose is 50 mg or 100 mg once daily, consider an increase of the dose by 50 mg. (see section **4.5 Interactions with other medicines and other forms of interactions**).

## 4.3 CONTRAINDICATIONS

JAYPIRCA is contraindicated in patients with known hypersensitivity to pirtobrutinib or any of the excipients listed in section **6.1 List of excipients**.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Infections**

Serious infections, including fatal events, have occurred in patients treated with JAYPIRCA. The most frequently reported Grade ≥3 infections were pneumonia, COVID-19 pneumonia, COVID-19, and sepsis. Consider prophylaxis in patients who are at increased risk for opportunistic infections. Based on the grade of infection and whether it occurs with neutropenia, dose modification may be required (see section **4.2 Dose and method of administration**).

**Haemorrhage**

Bleeding events, including fatal events, have occurred in patients treated with JAYPIRCA, with and without thrombocytopenia. Major bleeding events of Grade 3 or higher have been observed, including gastrointestinal and intracranial haemorrhage. Monitor patients for signs and symptoms of bleeding.

Patients receiving anticoagulant or antiplatelet agents are at increased risk of haemorrhage. The risks and benefits of anticoagulant or antiplatelet therapy should be considered when co-administered with JAYPIRCA. The use of JAYPIRCA has not been studied with warfarin or other vitamin K antagonists. Dose interruption may be required for Grade 3 or 4 bleeding events (see section **4.2 Dose and method of administration**).

The benefit-risk of withholding JAYPIRCA for 3 to 5 days pre- and post-surgery should be considered depending on the type of surgery and risk of bleeding.

**Cytopenias**

Grade 3 or 4 cytopenias, including neutropenia, anaemia, and thrombocytopenia, have occurred in patients treated with JAYPIRCA. Monitor complete blood counts during treatment as medically indicated. Based on the grade of cytopenia, dose modification may be required (see section **4.2 Dose and method of administration**).

**Atrial fibrillation/flutter**

Atrial fibrillation and atrial flutter have been observed in patients treated with JAYPIRCA, particularly in patients with a history of atrial fibrillation and/or multiple cardiovascular comorbidities. Monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an electrocardiogram (ECG) as medically indicated. Based on the grade of atrial fibrillation or atrial flutter, dose modification may be required (see section **4.2 Dose and method of administration**).

**Second primary malignancies**

Second primary malignancies have occurred in patients treated with JAYPIRCA, with the most frequent types being non-melanoma skin cancers. Patients should be monitored for the appearance of skin cancers and advise protection from sun exposure.

**Tumour lysis syndrome**

Tumour lysis syndrome (TLS) has been reported rarely with JAYPIRCA therapy. Patients at high risk of TLS are those with high tumour burden prior to treatment. Patients should be assessed for possible risk of TLS and closely monitored as clinically indicated.

**Use in the elderly**

No dose adjustment is required based on age (see section **5.2 Pharmacokinetic properties**).

**Paediatric use**

The safety and efficacy of JAYPIRCA in children and adolescents aged less than 18 years have not been established. No data are available.

**Effects on laboratory tests**

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pirtobrutinib is primarily metabolised by CYP3A4, UGT1A8, and UGT1A9. There was no clinically meaningful impact of CYP3A modulation on pirtobrutinib exposures in healthy subjects.

**Potential for other drugs to affect pirtobrutinib**

CYP3A inhibitors

In a clinical study, itraconazole, a strong CYP3A4 inhibitor, increased the AUC of pirtobrutinib by 48% and did not change $C_{max}$ of pirtobrutinib. This increase in pirtobrutinib exposure is not clinically meaningful. Therefore, no dose adjustment of JAYPIRCA is necessary with CYP3A inhibitors.

Moderate and strong CYP3A inducers

Coadministration of a single 200 mg dose of pirtobrutinib with rifampin (a strong CYP3A inducer) decreased the AUC of pirtobrutinib by 71% (see section **4.2 Dose and method of administration**).

If the current pirtobrutinib dose is 200 mg, consider increasing the dose to 300 mg once daily when co-administering with moderate or strong CYP3A inducers.

P-gp and BCRP inhibitors

*In vitro* studies indicated that pirtobrutinib is a substrate of P-gp and BCRP.

**Potential for Pirtobrutinib to Affect Other Drugs**

CYP2C8 substrates

Pirtobrutinib is a moderate inhibitor of CYP2C8. Pirtobrutinib increased the AUC and $C_{max}$ of repaglinide (a substrate of CYP2C8) by 130% and 98%, respectively. Use caution when co-administering pirtobrutinib with CYP2C8 substrates (e.g. enzalutamide, loperamide, montelukast, paclitaxel, pioglitazone, and repaglinide).

BCRP substrates

Pirtobrutinib is a moderate inhibitor of BCRP. Pirtobrutinib increased the AUC and $C_{max}$ of rosuvastatin (a sensitive BCRP substrate) by 140% and 146%, respectively. Use caution when co-administering pirtobrutinib with BCRP substrates. If co-administration with narrow therapeutic index BCRP substrates (e.g. high dose methotrexate, mitoxantrone) cannot be avoided, close clinical monitoring should be considered.

Sensitive P-gp substrates

Pirtobrutinib is a weak inhibitor of P-gp. Pirtobrutinib increased the AUC and $C_{max}$ of digoxin (a sensitive P-gp substrate) by 35% and 55%, respectively. Therefore, pirtobrutinib can increase the plasma concentrations of P-gp substrates. If co-administration with narrow

therapeutic index P-gp substrates (e.g dabigatran etexilate and digoxin) cannot be avoided, close clinical monitoring should be considered.

Sensitive CYP2C19 substrates

Pirtobrutinib is a weak inhibitor of CYP2C19. Pirtobrutinib increased the AUC and $C_{max}$ of omeprazole (a CYP2C19 substrate) by 56% and 49%, respectively. Therefore, pirtobrutinib can increase the plasma concentrations of CYP2C19 substrates. If co-administration with narrow therapeutic index CYP2C19 substrates (e.g. phenobarbital and mephenytoin) cannot be avoided, close clinical monitoring should be considered.

Sensitive CYP3A substrates

Pirtobrutinib is a weak inhibitor of CYP3A. Pirtobrutinib increased the AUC and $C_{max}$ of orally administered midazolam (a sensitive CYP3A substrate) by 70% and 58%, respectively. Pirtobrutinib did not have a clinically meaningful effect on the exposure of intravenously administered midazolam. Therefore, pirtobrutinib can increase the plasma concentrations of CYP3A substrates. If co-administration with narrow therapeutic index CYP3A substrates (e.g. alfentanil, midazolam, tacrolimus) cannot be avoided, close clinical monitoring should be considered.

In vitro Drug Interaction Investigations

Pirtobrutinib inhibits CYP2C8, CYP2C9 and CYP3A4 *in vitro* and minimally inhibits CYP1A2, CYP2B6, CYP2C19 or CYP2D6 at 60 μM. In vitro pirtobrutinib induces CYP3A4, CYP3A5, CYP2C19, and CYP2B6.

Pirtobrutinib minimally inhibits UGT1A1 *in vitro* with an IC50 = 18 μM.

Pirtobrutinib is an *in vitro* inhibitor of P-gp and BCRP.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

There is no data on the effect of pirtobrutinib on human fertility.

Fertility was unaffected in male and female rats given oral pirtobrutinib doses up to 500 mg/kg, twice daily (1000 mg/kg/day) prior to and during mating through gestation day 6. The relative exposure (AUC) for male and female rats was 0.3- and 2.5-times those in patients at the recommended dose of 200 mg per day. Given that clinical exposures could not be reached in male rats during fertility studies, possibility of effects on male fertility cannot be ruled out; however, it is considered less likely.

### Use in pregnancy

Pregnancy Category D.

JAYPIRCA is not recommended during pregnancy. Based on findings from animal studies, JAYPIRCA can cause fetal harm when administered to a pregnant woman.

In an embryofetal development study, oral (twice daily) administration of pirtobrutinib to pregnant rats during organogenesis resulted in decreased fetal weight, embryo-fetal

mortality, and fetal malformations (dilated ureters, absent kidneys, malpositioned ovaries, misshapen sternebrae) at maternal exposures (AUC) slightly higher to those in patients at the recommended dose of 200 mg.

**Use in lactation**

There are no data on the presence of pirtobrutinib in human milk, effects of pirtobrutinib on the breastfed child, or the effects of pirtobrutinib on milk production. Breastfeeding should be discontinued during treatment with JAYPIRCA and for 1 week after the last dose of JAYPIRCA.

**Women of childbearing potential/Contraception in males and females**

Based on findings in animals and the genotoxicity of pirtobrutinib (see section **5.3 Preclinical safety data**), pirtobrutinib can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should use an effective method of contraception during treatment and for 5 weeks after the last dose of JAYPIRCA. Men are advised to use an effective method of contraception and not father a child during treatment and for 3 months after the last dose of JAYPIRCA.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies have been conducted to determine the effects of pirtobrutinib on the ability to drive or use machines.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Summary of safety profile**

The safety profile of pirtobrutinib is based on integrated data from 704 patients with B-cell malignancies treated with JAYPIRCA as monotherapy 200 mg daily starting dose with no dose escalation in a phase 1/2 clinical study, and from patients treated with JAYPIRCA monotherapy in a phase 3 study. Median duration of exposure was 11.8 months.

The most common adverse events (reported in more than 2 patients) leading to dose reduction are neutrophil count decreased (1.4%), platelet count decreased (0.4%), neutropenia (0.9%), diarrhoea (0.4%), and fatigue (0.4%).

The most common adverse events (reported in more than 2 patients) leading to dose discontinuation are COVID-19 pneumonia (1.1%), pneumonia (0.9%), COVID-19 (0.7%), anaemia (0.7%), neutropenia (0.6%), and platelet count decreased (0.4%).

Serious adverse reactions associated with JAYPIRCA have occurred in 7.2% of patients and the most common serious events (occurring in ≥1% of patients) included pneumonia (1.6%) and febrile neutropenia (1.3%).

Fatal adverse reactions have been observed in 0.7% of patients (5 patients) including in 0.3% for COVID-19 pneumonia (2 patients), in 0.1% for septic shock (1 patient), and in 0.3% for respiratory failure (2 patients).

**CLL/SLL**

In an open-label phase 3 study, 238 patients with CLL/SLL previously treated with a BTK inhibitor were randomised in a 1:1 ratio. Of these, a total 116 patients were treated to receive JAYPIRCA once daily at a dose of 200 mg until disease progression or unacceptable toxicity or Investigator's choice.

**Table 2** provides a summary of the treatment-emergent adverse events occurring in the phase 3 CLL/SLL patients treated with JAYPIRCA as monotherapy.

**Table 2 Summary of treatment-emergent adverse events occurring in ≥10% of patients receiving Pirtobrutinib and idelalisib combined with rituximab or bendamustine combined with rituximab**

| Event any grade | Arm A | Arm B | | |
|---|---|---|---|---|
| | Pirtobrutinib (N=116) N (%) | IdelaR or BendaR (N=109) N (%) | IdelaR (N=77) N (%) | BendaR (N=32) N (%) |
| **Infections and infestations** | | | | |
| Pneumonia | 26 (22.4) | 13 (11.9) | 12 (15.6) | 1 (3.1) |
| COVID-19 | 15 (12.9) | 20 (18.3) | 17 (22.1) | 3 (9.4) |
| Upper respiratory tract infection | 12 (10.3) | 7 (6.4) | 6 (7.8) | 1 (3.1) |
| **General disorders and administration site conditions** | | | | |
| Pyrexia | 15 (12.9) | 29 (26.6) | 27 (35.1) | 2 (6.3) |
| Fatigue | 13 (11.2) | 22 (20.2) | 18 (23.4) | 4 (12.5) |
| Oedema peripheral | 13 (11.2) | 7 (6.4) | 6 (7.8) | 1 (3.1) |
| **Blood and lymphatic system disorders** | | | | |
| Anaemia | 23 (19.8) | 19 (17.4) | 11 (14.3) | 8 (25.0) |
| Neutropenia | 21 (18.1) | 17 (15.6) | 12 (15.6) | 5 (15.6) |
| **Gastrointestinal disorders** | | | | |
| Diarrhoea | 19 (16.4) | 34 (31.2) | 31 (40.3) | 3 (9.4) |
| Nausea | 13 (11.2) | 22 (20.2) | 13 (16.9) | 9 (28.1) |
| Vomiting | 8 (6.9) | 19 (17.4) | 13 (16.9) | 6 (18.8) |
| Constipation | 7 (6.0) | 12 (11.0) | 8 (10.4) | 4 (12.5) |
| **Investigations** | | | | |
| Neutrophil count decreased | 9 (7.8) | 19 (17.4) | 10 (13.0) | 9 (28.1) |
| Aspartate aminotransferase increased | 6 (5.2) | 14 (12.8) | 14 (18.2) | 0 |
| Alanine aminotransferase increased | 4 (3.4) | 19 (17.4) | 18 (23.4) | 1 (3.1) |
| Weight decreased | 4 (3.4) | 18 (16.5) | 13 (16.9) | 5 (15.6) |
| **Nervous system disorders** | | | | |
| Headache | 13 (11.2) | 16 (14.7) | 13 (16.9) | 3 (9.4) |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 19 (16.4) | 19 (17.4) | 17 (22.1) | 2 (6.3) |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 5 (4.3) | 14 (12.8) | 11 (14.3) | 3 (9.4) |
| **Injury, poisoning and procedural complications** | | | | |
| Infusion related reaction | 0 (0.0) | 19 (17.4) | 9 (11.7) | 10 (31.3) |

IdelaR= idelalisib combined with rituximab
BendaR=bendamustine combined with rituximab

**Tabulated list of adverse reactions**

A summary of adverse drug reactions from the integrated data associated with JAYPIRCA monotherapy is provided in **Table 3**.

**Table 3 Adverse reactions in patients with B-cell malignancies**

| **System Organ Class**<br>**Preferred Term / Event** | **All grades[a] (%)**<br>**N=704** | **Grade ≥3[b] (%)**<br>**N=704** |
|---|---|---|
| *Blood and lymphatic system disorders* | | |
| Neutropenia[c] | Very common (26.4) | Very common (22.6) |
| Anaemia[c] | Very common (18.5) | Very common (10.2) |
| Thrombocytopenia[c] | Very common (15.2) | Common (8.5) |
| Lymphocytosis[c] | Common (6.3) | Common (3.8) |
| *Gastrointestinal disorders* | | |
| Diarrhoea | Very common (22.7) | Common (1.0) |
| Nausea | Very common (15.8) | Uncommon (0.3) |
| Abdominal pain | Very common (10.2) | Uncommon (0.9) |
| *General disorders and administration site disorders* | | |
| Fatigue | Very common (25.6) | Common (1.7) |
| Oedema peripheral | Very common (10.9) | Uncommon (0.3) |
| *Infections and infestations* | | |
| Pneumonia | Very common (12.1) | Common (8.4) |
| Upper respiratory tract infection | Common (8.7) | (0) |
| Urinary tract infection | Common (8.7) | Common (1.0) |
| *Injury, poisoning, and procedural complications* | | |
| Contusion | Very common (16.9) | Uncommon (0.1) |
| *Musculoskeletal and connective tissue disorders* | | |
| Arthralgia | Very common (13.8) | Common (1.0) |
| *Nervous system disorders* | | |
| Headache | Very common (11.8) | Uncommon (0.7) |
| *Renal and urinary disorders* | | |
| Haematuria | Common (3.6) | (0) |
| *Respiratory, thoracic and mediastinal disorders* | | |
| Epistaxis | Common (4.5) | (0) |
| *Skin and subcutaneous tissue disorders* | | |
| Rash[c] | Very common (17.3) | Uncommon (0.9) |
| Petechia | Common (5.3) | (0) |
| *Vascular disorders* | | |
| Haematoma | Common (1.7) | Uncommon (0.1) |

a Very common = ≥10%; Common = ≥1% and <10%
b Severity grade assignment based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
c Consolidated term

**Less common adverse reactions (Grade ≥3)**

Vomiting, pyrexia, decreased appetite.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

### 4.9 OVERDOSE

In the event of overdose, appropriate supportive treatments should be initiated according to the patient's clinical signs and symptoms. There is no known antidote for JAYPIRCA overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors.

ATC code: L01EL05.

**Mechanism of action**

Pirtobrutinib is a reversible, noncovalent inhibitor of BTK. BTK is a signalling protein of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Pirtobrutinib binds to wild type BTK as well as BTK harbouring C481 mutations leading to inhibition of BTK kinase activity.

**Pharmacodynamic effects**

Cardiac electrophysiology

The effect of a single 900 mg dose of pirtobrutinib on the corrected QT (QTc) interval was evaluated in a study with placebo and positive controls in 30 healthy subjects. The selected dose is equivalent to approximately 2 times higher than the concentrations achieved at steady state at the recommended dosage of 200 mg once daily. Pirtobrutinib had no clinically meaningful effect on the change in QT corrected for heart rate using Fridericia's formula (QTcF) interval (i.e., > 10 ms) and there was no relationship between pirtobrutinib exposure and change in QTc interval.

**Clinical trials**

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The efficacy of JAYPIRCA in patients with BTK-inhibitor pretreated CLL/SLL was evaluated in a randomised, multicenter, international, open-label, actively-controlled trial (BRUIN CLL-321, Study 20020). The trial enrolled 238 patients with CLL/SLL who were previously

treated with a BTK inhibitor. Patients were randomised in a 1:1 ratio to receive either JAYPIRCA given orally once daily at a dose of 200 mg until disease progression or unacceptable toxicity, or Investigator's choice:

- Idelalisib plus a rituximab product (IR): Idelalisib 150 mg orally twice daily until disease progression or unacceptable toxicity, in combination with 8 infusions of a rituximab product (375 mg/m$^2$ intravenously on Day 1 of Cycle 1, followed by 500 mg/m$^2$ every 2 weeks for 4 doses and then every 4 weeks for 3 doses), with a 28-day cycle length.
- Bendamustine plus a rituximab product (BR): Bendamustine 70 mg/m$^2$ intravenously (Day 1 and 2 of each 28-day cycle), in combination with a rituximab product (375 mg/m$^2$ intravenously on Day 1 of Cycle 1, then 500 mg/m$^2$ on Day 1 of subsequent cycles), for up to 6 cycles.

Randomisation was stratified by 17p deletion status and receipt of prior venetoclax treatment. Of the 238 patients total, 119 were assigned to JAYPIRCA monotherapy, 82 to IR and 37 to BR. After confirmed disease progression, patients randomised to IR or BR had the option to cross over to JAYPIRCA monotherapy. Baseline characteristics were similar between treatment arms. Overall, the median age was 67 years (range: 42 to 90 years) and 70% were male and 81% were White. Baseline ECOG performance status was 0 or 1 in 93% of patients and 44% of patients had Rai stage III or IV disease. Among those patients with central testing available, 57% (101 of 176 patients) had 17p deletion and/or TP53 mutation, 86% (164 of 190 patients) had unmutated IGHV, and 65% (97 of 149) had complex karyotype.

Patients received a median number of 3 prior lines of therapy (range: 1 to 13) with 57% having at least 3 prior therapies and 51% having had prior BCL2-inhibitor therapy. The most common prior BTK inhibitors received were ibrutinib (87%), acalabrutinib (16%), and zanubrutinib (7%). 70% of patients discontinued the most recent BTK inhibitor for refractory or progressive disease, 15% discontinued for toxicity, and 19% discontinued for other reasons.

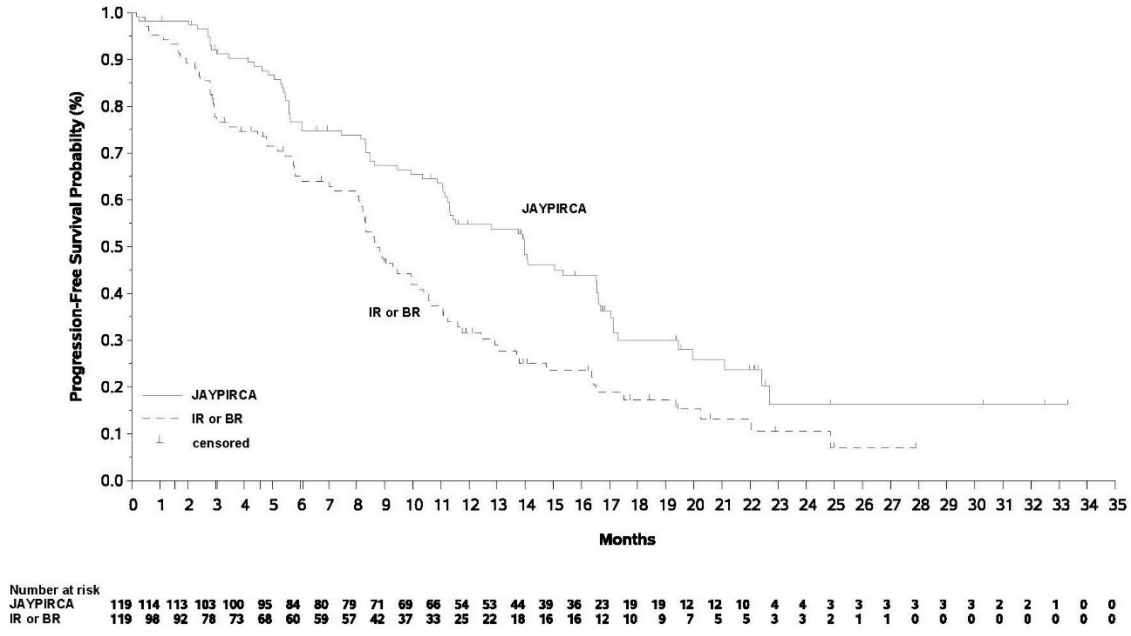
Efficacy was based on progression-free survival (PFS) of pirtobrutinib monotherapy versus investigator's choice arm as assessed by an Independent Review Committee (IRC). The study met its primary endpoint at the prespecified time of final analysis for IRC-assessed PFS (29 Aug 2023 cutoff). At an updated analysis (29 Aug 2024 cut-off) with a median follow-up of 19.4 months (range 0.03 to 33.3 months) for pirtobrutinib and 17.7 months (range 0.03 to 27.9 months) for the investigator's choice arm, improved IRC-assessed PFS was observed with pirtobrutinib, consistent with the primary analysis. Clinically meaningful efficacy results in favour of pirtobrutinib were observed across important subgroups, including patients who discontinued prior BTK inhibitor therapy due to intolerance or progression and irrespective of number and type of prior therapies. Efficacy results are presented in **Table 4**. The Kaplan-Meier curve for PFS is shown in **Figure 1**.

**Table 4 Efficacy Results per IRC in Patients with CLL Previously Treated with a BTK Inhibitor – ITT Population (BRUIN CLL-321)**

| | Pirtobrutinib 200 mg once daily (N = 119) | Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab (N = 119) |
|---|---|---|
| **Progression-free Survival** [a] | | |
| Number of Events, n | 74 (62%) | 79 (66%) |
| Disease Progression | 60 (50%) | 66 (55%) |
| Death | 14 (12%) | 13 (11%) |
| Median PFS (95% CI), months [b] | 14.0 (11.2, 16.6) | 8.7 (8.1, 10.4) |
| HR (95% CI)[c] | 0.54 (0.39, 0.75) | |
| P-value[d] | 0.0002 | |

CI, confidence interval; HR, hazard ratio.
Data cut-off date 29 Aug 2024
a Efficacy was assessed using the 2018 International Workshop for Chronic Lymphocytic Leukemia (iwCLL) guidelines.
b Based on Kaplan-Meier estimation.
c Based on stratified Cox proportional hazards model.
d 2-sided nominal p-value based on stratified log-rank test.

**Figure 1 Kaplan-Meier Curve of IRC-Assessed PFS in Patients with CLL Previously Treated with a BTK Inhibitor in BRUIN CLL-321**




With a median overall survival (OS) follow-up time of 20.4 months for pirtobrutinib and 19.2 months in investigator's choice arm, 38 patients (32.0%) in the pirtobrutinib arm and

32 patients (27.0%) in the investigator's choice arm died. Median OS was 29.7 months (95% CI: 27.1, NE) in the pirtobrutinib arm and not reached in the investigator's choice arm. The HR was 1.090 (95% CI: 0.679, 1.749; p = 0.7202). OS analysis may be confounded by the 50 out of 119 patients who crossed over from the investigator's choice arm to pirtobrutinib.

With the extended follow-up time, a continued improvement was seen in IRC- and Investigator-assessed overall response rate (ORR) and duration of response (DOR) in pirtobrutinib arm compared to the investigators choice arm. The IRC-assessed ORR of partial response (PR) or better was greater for pirtobrutinib (48.7%, 95% CI: 39.47, 58.07) than for the investigators choice arm(38.7%, 95% CI: 29.87, 48.02). Pirtobrutinib monotherapy improved DOR based on IRC assessments (HR = 0.641, 95% CI: 0.365, 1.126) and Investigator assessments (HR = 0.542, 95% CI: 0.337, 0.871) compared to investigators choice. The median IRC-assessed DOR of PR or better for pirtobrutinib was 13.77 months (95% CI: 11.07, NE) and for investigators choice was 11.86 months (95% CI: 8.25, 14.75).

In the supportive open-label, multicentre, multicohort Phase 1/2 study single-arm study Study 18001 (BRUIN) of oral pirtobrutinib, the safety and efficacy was evaluated in patients with B-cell malignancies, including CLL who have failed or were intolerant to standard of care., Study 18001 provides additional efficacy data to support the primary results from Study 20020, including evaluations of IRC-assessed ORR (primary endpoint) as well as secondary endpoints of OS and IRC-assessed DOR and PFS.

JAYPIRCA was given as monotherapy to 108 patients with CLL who were previously treated with at least two lines of therapy (including a BTK inhibitor and a BCL-2 inhibitor). The IRC-assessed ORR (primary analysis) was 72.6% (95% CI: 66.3, 78.4).

## 5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of pirtobrutinib were characterised in healthy subjects and in patients with cancer. Doses ranged from 25 mg to 300 mg once daily (0.125 to 1.5 times the recommended dosage of 200 mg once daily), up to single doses of 900 mg. Increases in plasma exposure were approximately dose proportional. Steady state was achieved within 5 days of once daily dosing, and in cancer patients the mean [coefficient of variation (CV %)] accumulation ratio after administration of 200 mg once daily was 1.63 (26.7%) based on AUC. Three patient factors were attributed to changes in pirtobrutinib PK: body weight, serum albumin, and absolute eGFR. An increase in body weight from 70 kg to 120 kg is predicted to increase pirtobrutinib clearance by 24%; a decrease in absolute eGFR from 90 mL/min to 30 mL/min is predicted to reduce pirtobrutinib clearance by 16%; and a decrease in serum albumin from 40 g/L to 30 g/L is predicted to increase pirtobrutinib clearance by 21%. These factors alone are unlikely to result in meaningful changes to pirtobrutinib PK and no dose adjustments are recommended.

The mean (CV %) steady-state AUC and $C_{max}$ were 92600 h*ng/mL (39%) and 6500 ng/mL (25%), respectively, at the recommended dosage of 200 mg once daily in cancer patients.

At the recommended dosage, pirtobrutinib achieves pharmacokinetic exposures that can exceed the BTK IC96 at trough and thus deliver tonic BTK target inhibition throughout the once daily dosing period, regardless of the intrinsic rate of BTK turnover.

**Absorption**

Absolute bioavailability of pirtobrutinib after a single oral 200 mg dose in healthy subjects was 85.5%. Median time to reach peak plasma concentration ($T_{max}$) is approximately 2 hours in both cancer patients and healthy subjects. There is no pH dependency for absorption.

Effect of food

A high-fat, high-calorie meal administered to healthy subjects decreased pirtobrutinib $C_{max}$ by 23% and delayed $T_{max}$ by 1 hour. There was no effect on pirtobrutinib AUC. Pirtobrutinib can be taken with or without food.

**Distribution**

The mean apparent central volume of distribution of pirtobrutinib is 34.2 L in cancer patients. The plasma protein binding is 96% and was independent of concentration between 0.5 and 50 μM. In plasma from healthy subjects and subjects with severe renal impairment, the protein binding was 96%. Mean blood-to-plasma ratio is 0.79.

**Metabolism**

Hepatic metabolism is the main route of clearance for pirtobrutinib. Pirtobrutinib is metabolised to several inactive metabolites by CYP3A4, UGT1A8, and UGT1A9.

**Excretion**

The mean apparent clearance of pirtobrutinib is 2.05 L/h with an effective half-life of approximately 19.9 hours. Following a single radiolabeled dose of pirtobrutinib 200 mg to healthy subjects, 37% of the dose was recovered in faeces (18% unchanged) and 57% in urine (10% unchanged).

**Special populations**

Age, gender, race, and body weight

Based on a population pharmacokinetic analysis in patients with cancer, age (range 22-95 years), gender (523 males and 257 females), and body weight (range 35.7-152 kg) had no overall effect on the exposure of pirtobrutinib.

Renal impairment

There was no overall effect of renal impairment on the pharmacokinetics of pirtobrutinib in otherwise healthy subjects. Patients on dialysis have not been studied.

Hepatic impairment

In a hepatic impairment study, there was no overall effect of hepatic impairment (Child-Pugh A, B, and C) on the pharmacokinetics of pirtobrutinib compared to normal hepatic function.

### 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

Pirtobrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay up to 5000 µg/plate. Pirtobrutinib was aneugenic in two *in vitro* micronucleus assays using human peripheral blood lymphocytes. Pirtobrutinib had no effect in an *in vivo* rat bone marrow micronucleus assay at doses up to 2000 mg/kg, which is approximately 0.5-fold in male rats and 3.8-fold in female rats than human exposure ($C_{max}$) at 200 mg.

**Carcinogenicity**

Carcinogenicity studies have not been conducted with pirtobrutinib.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Croscarmellose sodium
Hypromellose Acetate Succinate
Lactose Monohydrate
Magnesium Stearate
Microcrystalline Cellulose
Silicon Dioxide

Film coating

Hypromellose
Titanium dioxide
Triacetin
Indigo carmine aluminium lake

### 6.2 INCOMPATIBILITIES

Not applicable.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in original container.

## 6.5 NATURE AND CONTENTS OF CONTAINER

**JAYPIRCA 50 mg film coated tablets**

Polyvinylchloride (PVC)/polychlorotrifluoroethylene (PCTFE) blisters sealed with an aluminium foil in packs of 30 film-coated tablets.

**JAYPIRCA 100 mg film-coated tablets**

Polyvinylchloride (PVC)/polychlorotrifluoroethylene (PCTFE) blisters sealed with an aluminium foil in packs of 30, or 60 film-coated tablets.

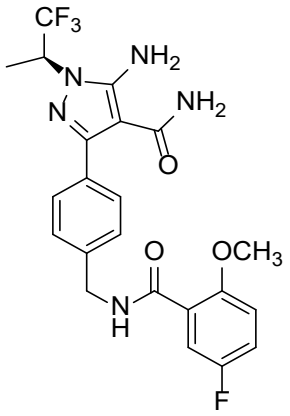
Not all pack sizes may be available.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**




**CAS number**

2101700-15-4

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Medicine

# 8 SPONSOR

Eli Lilly Australia Pty Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
1800 454 559

# 9 DATE OF FIRST APPROVAL

05 March 2026

# 10 DATE OF REVISION

## 10.1 SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| **All** | New entity |

JAYPIRCA® is a registered trademark of Eli Lilly and Company