ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Jaypirca 50 mg film-coated tablets
Jaypirca 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jaypirca 50 mg film-coated tablets

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 100 mg film-coated tablets

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.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Jaypirca 50 mg film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton’s tyrosine kinase (BTK) inhibitor.

Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a BTK inhibitor.

4.2 Posology and method of administration

Jaypirca therapy should be initiated and supervised by physicians experienced in the use of anticancer therapies.

Posology

The recommended dose is 200 mg pirtobrutinib once daily (QD).

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

Asymptomatic lymphocytosis is not regarded as an adverse reaction, and patients experiencing this event should continue taking Jaypirca.

In the clinical studies, adverse events in a limited number of patients were managed by dose reduction (see section 5.1).

Treatment should be continued until disease progression or unacceptable toxicity.

Missed dose
If more than 12 hours have passed after a patient has missed a dose, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken. If vomiting occurs, the patient should not take an additional dose but continue with the next scheduled dose.

Special populations

Elderly
No dose adjustment is required based on age (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. There are no data in patients on dialysis (see section 5.2).

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

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

Method of administration

Jaypirca is for oral use.

The tablet should be swallowed whole with a glass of water to ensure consistent performance (patients should not chew, crush, or split tablets before swallowing) and can be taken with or without food. Patients should take the dose at approximately the same time every day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Infections

Serious infections, including fatal cases, have occurred in patients treated with Jaypirca. The most frequently reported Grade 3 or higher infections were pneumonia, COVID-19 pneumonia, COVID-19, and sepsis. Prophylactic antimicrobial therapy should be considered in patients who are at increased risk for opportunistic infections. Based on the grade of infection and whether it occurs with neutropenia, dose interruption may be required (see section 4.2).

Haemorrhage

Bleeding events, including fatal cases, have occurred in patients treated with Jaypirca, with and without thrombocytopenia. Major bleeding events of Grade 3 or higher, including gastrointestinal bleeding and intracranial haemorrhage have been observed. Patients should be monitored for signs and symptoms of bleeding. Patients receiving anticoagulant or antiplatelet agents may be at increased risk of haemorrhage. The risks and benefits of anticoagulant or antiplatelet therapy should be considered when co-administered with Jaypirca and consider additional monitoring for signs of bleeding. 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).

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

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia, anaemia and thrombocytopenia occurred in patients treated with Jaypirca. Complete blood counts should be monitored in patients during treatment as medically indicated. Based on the grade of cytopenia, dose interruption may be required (see section 4.2).

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. Signs and symptoms of atrial fibrillation and atrial flutter should be monitored in patients; obtain an electrocardiogram as medically indicated. Based on the grade of atrial fibrillation/atrial flutter, dose interruption may be required (see section 4.2).

Second primary malignancies

Second primary malignancies have commonly 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.

Contraception in women of childbearing potential and males

Based on findings in animals and the genotoxicity of pirtobrutinib (see section 5.3), pirtobrutinib can cause foetal 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 (see section 4.6).

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg daily dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pirtobrutinib is primarily metabolised by CYP3A4, UGT1A8, and UGT1A9.

Effects of other medicinal products on the pharmacokinetics of 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.

CYP3A inducers
In a clinical study, rifampin, a strong CYP3A inducer, decreased the AUC and C_{max} of pirtobrutinib by 71 % and 42 %, respectively. Though this decrease in pirtobrutinib exposure is not expected to be clinically meaningful, if possible avoid strong CYP3A inducers (e.g. rifampicin, carbamazepine, phenytoin).

Coadministration with medicinal products that are proton pump inhibitors
No clinically significant differences in pirtobrutinib pharmacokinetics were observed when administered concomitantly with omeprazole, a proton pump inhibitor.

Effects of pirtobrutinib on the pharmacokinetics of other medicinal products (increase in plasma concentration)

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. Therefore, since pirtobrutinib can increase the plasma concentrations of CYP2C8 substrates, caution is advised when co-administering with CYP2C8 substrates (e.g. repaglinide, dasabuvir, selexipag, rosiglitazone, pioglitazone, and montelukast).

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

P-gp substrates
Pirtobrutinib is a weak inhibitor of P-gp. Pirtobrutinib increased the AUC and C_{max} of digoxin (a 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.

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.

CYP3A substrates
Pirtobrutinib is a weak inhibitor of CYP3A. Pirtobrutinib increased the AUC and C_{max} of orally administered midazolam (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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Based on findings in animals and the genotoxicity of pirtobrutinib (see section 5.3), pirtobrutinib can cause foetal 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 Jayprica (see section 4.4).

Pregnancy

There are no data from the use of Jaypirca in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Jaypirca should not be used during pregnancy.

Breast-feeding

It is unknown whether pirtobrutinib is excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Jaypirca and for one week after the last dose of Jaypirca.

Fertility

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

4.7 Effects on ability to drive and use machines

Jaypirca has a minor influence on the ability to drive and use machines. Fatigue, dizziness, and asthenia have been reported in some patients during treatment with Jaypirca and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions of any grade are: neutropenia (27.7 %), fatigue (26.2 %), diarrhoea (23.8 %), anaemia (20.7 %), rash (18.4 %) and contusion (17.8 %).

The most common severe (Grade ≥ 3) adverse reactions are: neutropenia (23.9 %), anaemia (11.2 %), thrombocytopenia (9.7 %), and pneumonia (9.0 %).

The frequency of treatment discontinuation due to adverse reactions is 4.2 % and the frequency of dose reductions due to adverse reactions is 4.8 %.

The most common adverse reactions (reported in more than 2 patients) leading to dose reduction are neutropenia (2.5 %), rash (0.6 %), diarrhoea (0.4 %), fatigue (0.4 %) and thrombocytopenia (0.4 %). The most common adverse reactions (reported in more than 2 patients) leading to dose discontinuation are neutropenia (1.0 %), anaemia (1.0 %), pneumonia (0.9 %), thrombocytopenia (0.7 %) and rash (0.4 %).

Serious adverse reactions associated with Jaypirca have occurred in 19.4 % of patients and the most common serious adverse reactions (occurring in ≥1 % of patients) were pneumonia (8.0 %), neutropenia (3.2 %), anaemia (2.6 %), atrial fibrillation/atrial flutter (1.3 %) and urinary tract infection (1.0 %).

Fatal adverse reactions have been observed in 0.4 % of patients (3 patients) for pneumonia, in 0.3 % of patients (2 patients) for haemorrhage and in 0.1 % of patients (1 patient) for urinary tract infection.

Tabulated list of adverse reactions

Table 1 lists the adverse drug reactions (ADRs) associated with Jaypirca used as a monotherapy from clinical study data and post-marketing experience. The ADRs identified from clinical trials are based on pooled data from 690 patients treated with Jaypirca monotherapy 200 mg QD starting dose with no dose escalation in a phase 1/2 clinical study, and from patients treated with Jaypirca monotherapy 200 mg QD in a phase 3 study. Patients were treated for MCL, chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and other non-Hodgkin lymphoma (NHL). Patients were exposed to Jaypirca for a median duration of 12 months. ADRs are listed below by MedDRA body system organ class. Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 1: ADRs of patients treated with Jaypirca[a]

System organ class (MedDRA)	ADR	Frequency category (%) (All grades)	Grade ≥ 3[c] (%)
Infections and infestations	Pneumonia	Very common (13.8)	9.0
	Upper respiratory tract infection	Very common (10.1)	0.1
	Urinary tract infection	Common (9.9)	1.4
Blood and lymphatic system disorders	Neutropenia[b]	Very common (27.7)	23.9
	Anaemia[b]	Very common (20.7)	11.2
	Thrombocytopenia[b]	Very common (16.8)	9.7
	Lymphocytosis[b]	Common (6.4)	3.9
Nervous system disorders	Headache	Very common (12.6)	0.7

Cardiac disorders	Atrial fibrillation/atrial flutter	Common (3.8)	1.7
Vascular disorders	Haemorrhage[b]	Very common (20.3)	2.8
	Epistaxis	Common (5.2)	0
	Haematuria	Common (4.5)	0.1
	Haematoma	Common (1.7)	0.1
	Conjunctival haemorrhage	Common (1.7)	0.1
	Bruising[b]	Very common (19.7)	0.3
	Contusion	Very common (17.8)	0.1
	Petechiae	Common (5.7)	0
Gastrointestinal disorders	Diarrhoea	Very common (23.8)	1.0
	Nausea	Very common (16.7)	0.4
	Abdominal pain	Very common (10.4)	1.0
Hepatobiliary disorders	Hepatic enzyme increased	Not known	Not known
Skin and subcutaneous tissue disorders	Rash[b]	Very common (18.4)	1.2
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (14.6)	1.2
General disorders and administration site conditions	Fatigue	Very common (26.2)	1.9
	Oedema peripheral	Very common (11.6)	0.3

[a] Frequencies are derived from Jaypirca exposure in patients with B-cell malignancies

[b] Includes multiple adverse reaction terms

[c] Severity grade assignment based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

No maximum tolerated dose was reached in the phase 1 study in which patients received repeated doses up to 300 mg once daily. In healthy volunteer studies, no dose related toxicity was observed when a maximum single dose of 900 mg was administered. Signs and symptoms of pirtobrutinib overdose have not been established and there is no specific treatment for pirtobrutinib overdose. For patients who experience overdose, closely monitor and provide appropriate supportive treatment.

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 harboring 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 efficacy and safety

Mantle Cell Lymphoma
The efficacy of Jaypirca was evaluated in adult patients with MCL in a phase 1/2 multicenter, open label, single arm clinical study: Study 18001 (BRUIN). The study included two parts: a phase 1 dose escalation, in which the dose range of monotherapy pirtobrutinib of 25 mg to 300 mg once daily was investigated, and a phase 2 dose expansion. The primary objective of the phase 1 portion was to determine the recommended phase 2 dose of pirtobrutinib, which was found to be 200 mg once daily, with a maximum tolerated dose not being established. The primary objective of the phase 2 part was to assess the anti-tumor activity of pirtobrutinib based on overall response rate as assessed by an independent review committee. Patients received Jaypirca orally daily until disease progression or unacceptable toxicity.

Study 18001 enrolled and treated a total of 164 patients with a diagnosis of MCL and the primary analysis set (PAS) for the assessment of efficacy was based on the first 90 patients with MCL enrolled who had no known central nervous system (CNS) involvement, were treated with a prior BTK inhibitor, had received one or more doses of Jaypirca and had at least 1 site of radiographically assessable disease. The median age was 70 years (range: 46 to 87 years), 80 % were male, 84.4 % were White, 67.8 % had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 31.1 % had ECOG performance status of 1. Patients had a median number of 3 prior lines of therapy (range: 1 to 8), with the reason for discontinuation from the most recent prior BTK inhibitor therapy being progression in 81.1 % of patients and intolerance in 13.3 % of patients. 95.6 % of patients received prior anti-CD20 therapy, 87.8 % chemotherapy, 18.9 % autologous stem cell transplantation, 4.4 % allogenic stem cell transplantation, 15.6 % prior BCL2 inhibitor and 4.4 % received prior chimeric antigen receptor-modified T cells (CAR-T) therapy. 38.9 % patients had extranodal involvement and 26.7 % had tumour bulk greater than or equal to 5 cm. The simplified MCL International Prognostic Index (sMIPI) score was low in 22.2 %, intermediate in 55.6 % and high in 22.2 % of patients.

Of the 164 patients with MCL enrolled in Study 18001, 9 patients had a dose reduction, including 6 responders that were able to remain on therapy and maintain a durable response following dose reductions to 150 mg QD (3), 100 mg QD (2), and 50 mg QD (1).

The efficacy of Jaypirca was based on a response as assessed using 2014 Lugano criteria for malignant lymphoma. Efficacy results for patients that received at least one prior BTK inhibitor and included in the PAS are summarised in Table 2. For the 90 patients in the PAS, 79 received at least 1 dose of 200 mg QD. Of these 79 patients, 77 started at 200 mg QD, 1 dose escalated from a lower dose and 1 dose reduced from a higher dose. The median time on treatment was 5.24 months (range: 0.2 to 39.6 months). Among the 51 responders, the median time to response was 1.84 months (range: 1.0 to 7.5 months).

While subgroup analyses represent a limited number of patients, clinically meaningful efficacy results were observed across important subgroups, including patients that discontinued prior BTK inhibitor therapy due to intolerance or progression and irrespective of number and type of prior therapies.

Table 2: Summary of efficacy data in Study 18001 for MCL patients who received at least one prior BTK inhibitor

	Pirtobrutinib N=90
Objective response rate (Complete response + partial response)	
Rate – percent (95 % CI)	56.7 (45.8, 67.1)
CR – percent	18.9
PR – percent	37.8
Duration of response	
Median - months (95 % CI)	17.61 (7.29, 27.24)

Abbreviations: CI = confidence interval, NE= not estimable, CR = complete response, PR = partial response.
Data cut-off date: 29 July 2022. The median follow-up time for duration of response was 12.68 months.

Chronic Lymphocytic Leukaemia
The efficacy of Jaypirca in patients with BTK-inhibitor pretreated CLL was evaluated in a randomised, multicentre, 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/m2 intravenously on Day 1 of Cycle 1, followed by 500 mg/m2 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/m2 intravenously (Day 1 and 2 of each 28-day cycle), in combination with a rituximab product (375 mg/m2 intravenously on Day 1 of Cycle 1, then 500 mg/m2 on Day 1 of subsequent cycles), for up to 6 cycles.

Randomisation was stratified by 17p deletion status (yes/no) and receipt of prior venetoclax treatment (yes/no). 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), 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 15 % 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 cut-off). 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 compared to the investigator's choice arm, consistent with the primary analysis. Clinically meaningful efficacy results in favour of pirtobrutinib were observed across important subgroups, including patients who

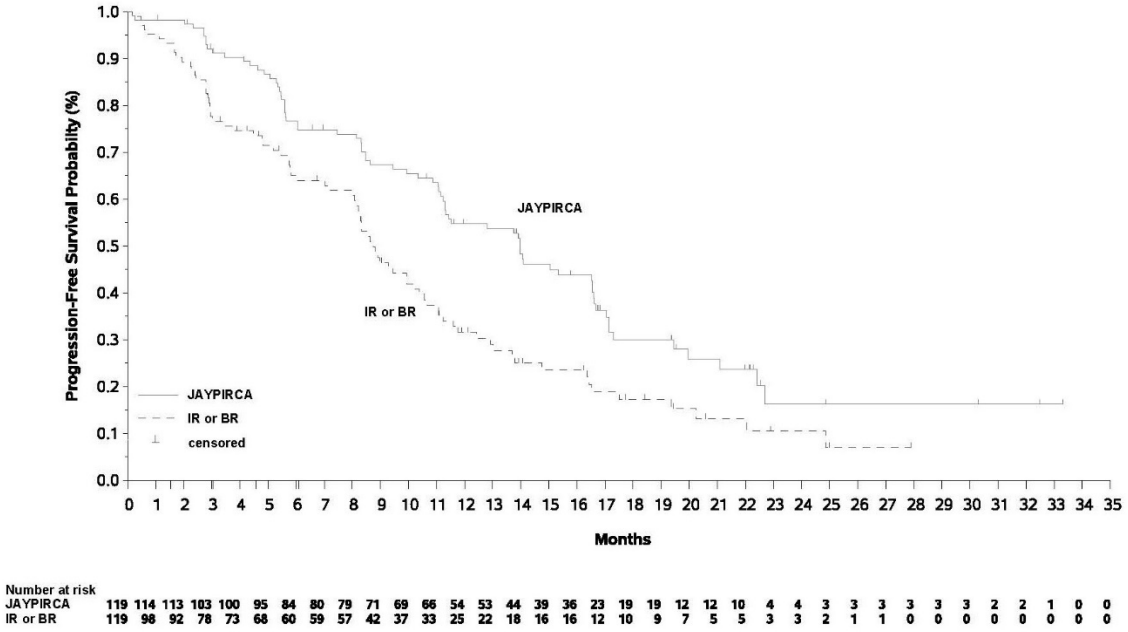
discontinued prior BTK inhibitor therapy due to intolerance or progression and irrespective of number and type of prior therapies. Efficacy results are presented in Table 3. The Kaplan-Meier curve for PFS is shown in Figure 1.

Table 3: Efficacy Results per IRC in Patients with CLL Previously Treated with a BTK Inhibitor – ITT Population (Study 20020)

	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 Study 20020



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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jaypirca in all subsets of the paediatric population in mature B-cell malignancies (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of pirtobrutinib were characterized 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 92 600 h*ng/mL (39 %) and 6 500 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 IC_{96} at trough and thus deliver tonic BTK target inhibition throughout the once daily dosing period, regardless of the intrinsic rate of BTK turnover.

Absorption

The absolute bioavailability of pirtobrutinib after a single oral 200 mg dose is 85.5 % in healthy subjects. The 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 the C_{max} of pirtobrutinib 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.

Biotransformation

Hepatic metabolism is the main route of clearance for pirtobrutinib. Pirtobrutinib is metabolised to several inactive metabolites by CYP3A4, UGT1A8 and UGT1A9. There was no clinically meaningful impact of CYP3A modulation on pirtobrutinib exposures.

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.

Co-administration with transport substrates/inhibitors
In vitro studies indicated that pirtobrutinib is a substrate of P-gp and BCRP.

Pirtobrutinib is an *in vitro* inhibitor of P-gp and BCRP. Pirtobrutinib affected the PK of digoxin, a P-gp substrate, and rosuvastatin, a BCRP substrate, in clinical studies (see section 4.5).

Elimination

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), race, gender, and body weight (range 35.7-152 kg) had no clinically meaningful effect on the exposure of pirtobrutinib.

Renal impairment
In a population PK analysis of cancer patients, patients with mild (eGFR 60 to < 90 ml/min) or moderate renal impairment (eGFR 30 to < 60 ml/min), pirtobrutinib clearance was 16 % to 27 % lower compared to clearance in patients with normal renal function, resulting in expected exposure of AUC = 94 100 ng*h/mL and C_{max} = 6 680 ng/mL in patients with mild renal impairment (16-19 % higher compared to patients with normal renal function) and AUC = 108 000 ng*h/mL and C_{max} = 7 360 ng/mL in patients with moderate renal impairment (28 to 36 % higher compared to patients with normal renal function).

In a clinical pharmacology study of otherwise healthy volunteers, apparent clearance was 35 % lower in four participants with severe renal impairment (eGFR 15 to < 30 ml/min) compared to eight participants with normal renal function (eGFR ≥ 90 ml/min), resulting in exposures of $AUC_{0\text{-}inf}$ = 115 000 ng*h/mL and C_{max} = 2 980 ng/mL (62 % higher and 7 % lower, respectively, compared to normal renal function).

Patients with end-stage renal disease receiving dialysis were not studied (see section 4.2).

Hepatic impairment
There were no clinically significant differences in the PK of pirtobrutinib for any degree of hepatic impairment (by Child-Pugh A, B, and C or any total bilirubin and any AST). In a dedicated hepatic impairment study mean AUC and C_{max} of pirtobrutinib were similar between subjects with mild hepatic impairment (Child-Pugh A) and subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh B) the AUC was 15 % lower compared to normal hepatic function and the C_{max} was similar. In subjects with severe hepatic impairment (Child-Pugh C) the AUC of pirtobrutinib was 21 % lower and mean C_{max} was 24 % lower compared to subjects with normal hepatic function. The fraction unbound (fu) for pirtobrutinib in subjects generally increased as

the severity of hepatic impairment increased. Therefore, after correcting pirtobrutinib PK exposure parameters with fu, there was no clinically significant difference observed in the unbound pirtobrutinib PK exposure parameters (AUCu and C_{max},u) between subjects with any degree of hepatic impairment and normal hepatic function.

Paediatric population
No pharmacokinetic studies were performed with pirtobrutinib in patients under 18 years of age.

5.3 Preclinical safety data

In the repeat-dose studies decreased T-cell dependent antibody response in rats (at 0.69-fold human exposure at the recommended dose of 200 mg based on AUC) and minimal to mild corneal lesions in dogs (at 0.42-fold human exposure) were observed. Mild to moderate vascular necrosis and vascular/perivascular inflammation in large pulmonary blood vessels were observed only in rats. These effects occurred at clinically relevant exposure levels.

Genotoxicity / Carcinogenicity

Pirtobrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay. 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 2 000 mg/kg (single dose), which is approximately 11-fold higher exposure (considering unbound C_{max} value in female animals) than human exposure at 200 mg.

Carcinogenicity studies have not been conducted with pirtobrutinib.

Embryotoxicity/ Teratogenicity

In animal reproduction studies, administration of pirtobrutinib to pregnant rats during organogenesis resulted in decreased foetal weight, embryo-foetal mortality, and foetal malformations at maternal exposures 3.0-fold human exposure at the recommended dose of 200 mg based on AUC.

Reproduction toxicity

No fertility studies have been conducted with pirtobrutinib. In repeat-dose toxicity studies of up to 3 months duration, pirtobrutinib had no effect on male reproductive organs at 0.69-fold and 0.42-fold human exposure in rats and dogs, respectively, at the recommended dose of 200 mg based on AUC. Pirtobrutinib had no effect on female reproductive organs at 4.0-fold and 0.42-fold human exposure in rats and dogs, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Hypromellose acetate succinate
Cellulose, microcrystalline
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate
Silica, colloidal hydrated

Film-coating
Hypromellose
Titanium dioxide
Triacetin

Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Jaypirca 50 mg film-coated tablets

Polyvinylchloride/polychlorotrifluoroethylene blisters sealed with an aluminium foil in packs of 28, 30 or 84 film-coated tablets.

Jaypirca 100 mg film-coated tablets

Polyvinylchloride/polychlorotrifluoroethylene blisters sealed with an aluminium foil in packs of 28, 30, 56, 60, 84 or 168 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83
3528 BJ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1738/001
EU/1/23/1738/002
EU/1/23/1738/003
EU/1/23/1738/004
EU/1/23/1738/005
EU/1/23/1738/006
EU/1/23/1738/007
EU/1/23/1738/008
EU/1/23/1738/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 October 2023
Date of latest renewal: 8 September 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lilly, S.A.
Avda. de la Industria, 30
28108 Alcobendas, Madrid
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of pirtobrutinib in the treatment of patients with mantle cell lymphoma (MCL), the clinical study report of the Phase 3 study LOXO-BTK-20019 (BRUIN MCL-321) comparing pirtobrutinib	31 December 2026

Description	Due date
to investigator choice of BTK inhibitor in patients with previously treated BTK inhibitor naïve MCL should be submitted by	

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 50 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jaypirca 50 mg film-coated tablets
pirtobrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg of pirtobrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
30 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83
3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1738/001 (28 film-coated tablets)
EU/1/23/1738/002 (30 film-coated tablets)
EU/1/23/1738/003 (84 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jaypirca 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 50 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jaypirca 50 mg tablets
pirtobrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jaypirca 100 mg film-coated tablets
pirtobrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of pirtobrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
60 film-coated tablets
84 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.,
Papendorpseweg 83,
3528 BJ Utrecht,
The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1738/004 (28 film-coated tablets)
EU/1/23/1738/005 (30 film-coated tablets)
EU/1/23/1738/006 (56 film-coated tablets)
EU/1/23/1738/007 (60 film-coated tablets)
EU/1/23/1738/008 (84 film-coated tablets)
EU/1/23/1738/009 (168 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jaypirca 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Jaypirca 100 mg tablets
pirtobrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Jaypirca 50 mg film-coated tablets
Jaypirca 100 mg film-coated tablets
pirtobrutinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Jaypirca is and what it is used for

Jaypirca is a cancer medicine that contains the active substance pirtobrutinib. It belongs to a class of medicines called Bruton's tyrosine kinase (BTK) inhibitors.

It is used on its own (monotherapy) to treat the following blood cancers in adult patients who have been previously treated with another BTK inhibitor:
- Mantle cell lymphoma (MCL) . MCL is an aggressive (fast growing) cancer of a type of white blood cell called B-cells. B-cells are part of the immune system (the body's natural defences). This medicine is used when the cancer has come back (relapsed), or treatment has not worked (refractory).
- Chronic lymphocytic leukaemia (CLL): a type of cancer affecting white blood cells called lymphocytes. This medicine is used when the cancer has come back (relapsed), or treatment has not worked (refractory).

How Jaypirca works
Jaypirca works by blocking BTK, a protein in the body that helps MCL and CLL cells grow and survive. By blocking BTK, Jaypirca helps to kill these cells and can reduce their number, which can slow down the worsening of the cancer.

2. What you need to know before you take Jaypirca

Do not take Jaypirca
- If you are allergic to pirtobrutinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Jaypirca:
- If you have an infection or are at an increased risk of developing an opportunistic infection (infections seen in patients with a weakened immune system). Your doctor may give you medicines to treat or prevent infections.
- If you have or ever had unusual bruising or bleeding or are on any medicines or supplements that could increase your risk of bleeding. See section "Other medicines and Jaypirca" below.
- If you recently had low counts of red blood cells (anaemia), neutrophils (a type of white blood cell that fights infections) or platelets (components that help the blood to clot).
- If you have recently had any surgery or are planning to have surgery. Your doctor may ask you to stop taking Jaypirca for a short time (3 to 5 days) before and after your surgery.
- If you have or ever had an irregular heartbeat or have other heart and/or blood vessel problems, such as high blood pressure, history of a heart attack or have heart valve damage.

You may get infections during treatment with Jaypirca. Contact your doctor if you have fever, chills, weakness, confusion, body aches, cough, cold or flu symptoms, feel tired, feel short of breath, have pain or burning feeling when passing urine. These could be signs of an infection.

Talk to your doctor if you develop a new lesion or any change in the appearance of an area on the skin, as treatment with Jaypirca may increase your risk of developing skin cancer. Use sun protection and make regular skin examinations.

Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, known as tumour lysis syndrome (TLS), have been reported rarely during treatment with Jaypirca. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare professional may do blood tests to check for TLS.

Your doctor will monitor you for the signs and symptoms of bleeding (see section 4) and check your blood cell counts as needed during treatment.

Your doctor may monitor your heart rhythm for any irregularities throughout treatment.

Children and adolescents
Do not give Jaypirca to children and adolescents aged less than 18 years. This is because it has not been studied in this age group.

Other medicines and Jaypirca
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Jaypirca may make you bleed more easily. This means you should tell your doctor if you take other medicines that increase your risk of bleeding. This includes medicines such as:
- acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen and naproxen,
- anticoagulants such as warfarin, heparin and other medicines for treating or preventing blood clots,
- supplements that may increase your risk of bleeding such as fish oil, vitamin E or flaxseed.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking Jaypirca.

Tell your doctor or pharmacist if you take any of the following medicines as Jaypirca may affect how well these medicines work:
- Repaglinide, rosiglitazone, or pioglitazone (used to treat diabetes)
- Dasabuvir (used for Hepatitis C infection)
- Selexipag (used to treat a type of high blood pressure in the lungs called pulmonary arterial hypertension)
- Rosuvastatin (a statin, a type of medicine to treat high cholesterol)
- Montelukast (used to treat asthma)
- Digoxin (used to treat heart disorders)
- Dabigatran etexilate (an anticoagulant, a type of medicine used to prevent blood clots)
- Phenobarbital (a barbiturate, a type of medicine used to treat seizures)
- Mephenytoin, phenytoin, and carbamazepine (a type of medicine used to treat seizures)
- Midazolam (sedative),
- Alfentanil (medicine used for anesthesia)
- Tacrolimus (used to prevent organ rejection and skin conditions)
- Rifampicin (antibiotic)
- Methotrexate (medicine used to treat other cancers or immune system disorders)
- Mitoxantrone (medicine used to treat other cancers)

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not use Jaypirca during pregnancy. If you are a woman of childbearing age, you must use an effective method of contraception during treatment and for 5 weeks after your last dose of Jaypirca. Tell your doctor immediately if you become pregnant.

If you are a man, you must use an effective method of contraception during treatment and for 3 months after your last dose of Jaypirca.

Do not breast-feed while taking Jaypirca and for one week after your last dose of Jaypirca. It is unknown whether Jaypirca passes into breast milk.

It is unknown whether Jaypirca will have an effect on fertility. Talk to your doctor or pharmacist for advice if you are planning to have a baby.

Driving and using machines
Jaypirca has a minor effect on your ability to drive and use machines. You may feel tired, dizzy or weak after taking Jaypirca and this may affect your ability to drive or use machines.

Jaypirca contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Jaypirca contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 200 mg daily dose, that is to say essentially ‘sodium-free’.

3. How to take Jaypirca

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Jaypirca is 200 mg once a day.

If you get certain side effects while you are taking Jaypirca, your doctor may stop treatment temporarily or lower your dose.

Jaypirca should be taken at about the same time every day. You can take the tablets with or without food. Swallow the tablet whole with a glass of water. Do not chew, crush, or split tablets before swallowing to ensure you receive the correct dose.

If you take more Jaypirca than you should
If you have taken more Jaypirca than you should, contact a doctor or go to a hospital immediately for advice. Take the tablets and this leaflet with you. Medical treatment may be necessary.

If you forget to take Jaypirca
- If less than 12 hours have passed after your usual time for taking a dose: Take the missed dose right away. Take the next dose at your usual scheduled time the next day.
- If more than 12 hours have passed after your usual time for taking a dose: Skip the missed dose. Take the next dose at your usual scheduled time the next day.
- Do not take a double dose of Jaypirca to make up for a forgotten dose. Take the next dose at your usual scheduled time.
- Do not take a double dose of Jaypirca if you experience vomiting. Take the next dose at your scheduled usual time.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Jaypirca and tell a doctor right away if you notice any of the following side effects:

- itchy bumpy rash, difficulty breathing, swelling of your face, lips, tongue or throat – you may be having an allergic reaction to the medicine.

Contact your doctor immediately if you experience any of the following side effects:
- fever, chills, feeling weak or confused, cough, cold or flu symptoms, shortness of breath, pain or burning feeling when passing urine; these could be signs of an infection. These could include the very common side effects (may affect more than 1 in 10 people) of infection of the lung (pneumonia), nose, sinus or throat (upper respiratory tract infection) or infection of the urinary tract (may affect up to 1 in 10 people).
- bleeding, which may affect more than 1 in 10 people. Signs could include the common side effects (may affect up to 1 in 10 people) of nosebleeds, collection of blood under tissue (haematoma) and bleeding in the tissue lining the eye. Other signs of bleeding may include pink or brown urine, black stools or stools with blood, bleeding gums, vomiting or coughing up blood.
- irregular heartbeats, weak or uneven pulse, light headedness, shortness of breath, chest discomfort as these are symptoms of heart rhythm problems (may affect up to 1 in 10 people).

Tell your doctor, pharmacist, or nurse if you notice any of the following other side effects:

Very common (may affect more than 1 in 10 people)
- tiredness (fatigue)
- low levels of neutrophils (a type of white blood cell that fights infection; neutropenia)
- frequent or loose stools (diarrhoea)
- bruising
- contusion

- feeling sick (nausea)
- low red blood cell counts (anaemia), which can cause tiredness and pale skin
- joint pain (arthralgia)
- low blood platelet counts (cells that help blood to clot; thrombocytopenia)
- rash
- belly (abdominal) pain
- swollen hands, ankles or feet
- headache

Common (may affect up to 1 in 10 people)
- lymphocytosis (a higher-than-normal amount of lymphocytes, a type of white blood cell, in the blood)
- tiny blood spots under the skin (petechiae)

Not known (frequency cannot be estimated from the available data)
- increased levels of liver enzymes

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Jaypirca

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Jaypirca contains
The active substance is pirtobrutinib. Each film-coated tablet contains 50 or 100 mg pirtobrutinib.
The other ingredients are:
- Tablet core: hypromellose acetate succinate; cellulose, microcrystalline; lactose monohydrate (see section 2 “Jaypirca contains lactose”); croscarmellose sodium (see section 2 “Jaypirca contains sodium”); magnesium stearate; silica, colloidal hydrated.
- Tablet film-coat: hypromellose; titanium dioxide; triacetin; indigo carmine (E132).

What Jaypirca looks like and contents of the pack
Jaypirca 50 mg is supplied as a blue, arc-triangle shaped film-coated tablet (tablet) debossed with “Lilly 50” on one side and “6902” on the other side. It is available in blister packs of 28, 30 or 84 film-coated tablets.

Jaypirca 100 mg is supplied as a blue, round tablet debossed with “Lilly 100” on one side and “7026” on the other side. It is available in blister packs of 28, 30, 56, 60, 84 or 168 film-coated tablets.

Not all the pack sizes may be marketed.

Marketing Authorisation Holder
Eli Lilly Nederland B.V.,
Papendorpseweg 83,
3528BJ Utrecht,
The Netherlands.

Manufacturer
Lilly S.A.,
Avda. de la Industria 30,
28108 Alcobendas,
Madrid, Spain.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

This medicine has been given 'conditional approval'.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for pirtobrutinib, the scientific conclusions of PRAC are as follows:

In view of available data on pirtobrutinib from clinical trials and spontaneous reports, including cases with a close temporal relationship, including positive de-challenges and re-challenges (of which one case had multiple positive rechallenges), the PRAC considers a causal relationship between pirtobrutinib and hepatic enzyme increased is at least a reasonable possibility. The PRAC concluded that the product information of products containing pirtobrutinib should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for pirtobrutinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing pirtobrutinib is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.