swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Jaypirca

International non-proprietary name:	pirtobrutinib
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	50 mg, 100 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Eli Lilly (Suisse) SA
Marketing authorisation no.:	68733
Decision and decision date:	extension of therapeutic indication approved on 23 September 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

3L	Third-line
AE	Adverse event
AUC	Area under the plasma concentration-time curve
BCL2(i)	B-cell lymphoma 2 (inhibitor)
BR	Bendamustin + rituximab
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum observed plasma/serum concentration of drug
DCO	Data cut-off
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IR	Idelalisib + rituximab
IRC	Independent review committee
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
QD	Once daily (Latin: quaque die)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 3 May 2022.

2.2 Indication and dosage

2.2.1 Requested indication

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 Bruton's tyrosine kinase (BTK) inhibitor.

2.2.2 Approved indication

Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have received at least two prior lines of therapy, including a BTK inhibitor (see "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	2 April 2024
Formal control completed	1 May 2024
List of Questions (LoQ)	29 August 2024
Response to LoQ	6 February 2025
Preliminary decision	17 April 2025
Response to preliminary decision	27 May 2025

2nd Preliminary decision	3 July 2025
Response to 2nd preliminary decision	25 August 2025
Final decision	23 September 2025
Decision	approval

3 Medical context

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the western world with an average incidence of about 4.2/100,000/year, which increases to >30/100,000/year at >80 years. While the median age at diagnosis is 72 years, approximately 10% of CLL patients are reported to be younger than 55 years[1]. Despite recent therapeutic progress, CLL remains an incurable disease in most cases. Preferred initial therapy includes continuous covalent BTK inhibitor (BTKi)-based regimens and fixed-duration combined BCL2 inhibitor (BCL2i) + anti-CD20 monoclonal antibody. Patients whose disease is treatment-refractory or who relapse after these therapies have limited options and, in many cases, a poor prognosis, with 2-year overall survival (OS) rates dropping below 50% in high-risk disease settings[2].

Because the most frequent mechanism of acquired resistance to covalent BTKi is the occurrence of point mutations of the cysteine residues 481 of BTK, non-covalent BTKi pirtobrutinib, which binds non-covalently to BTK at non-C481 sites, might be a therapeutic approach in covalent BTKi-resistant CLL. The present application proposes the use of pirtobrutinib for the treatment of CLL after prior BTKi therapy. In support of its application, the applicant submitted data from pivotal randomised, controlled phase 3 study LOXO-BTK-20020 (study 20020), comparing pirtobrutinib monotherapy (arm A) with investigator-choice therapeutic options idelalisib + rituximab (IR) and bendamustine + rituximab (BR) [arm B].

[1] Eichhorst B et al. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia. Ann Oncol 2024;35:762-768.
[2] Soumerai JD et al. Risk Model for Overall Survival in Relapsed or Refractory Chronic Lymphocytic Leukaemia in the Era of Targeted Therapies. Lancet Haematol 2019;6: e366-e374.

4 Nonclinical aspects

The applicant submitted two new nonclinical studies, a six-month repeat-dose toxicity study in rats and a nine-month repeat-dose toxicity study in dogs. These studies were not performed to support the requested new indication, but with the intention of conducting a clinical development programme outside the scope of ICH S9.
There was a new finding in the six-month study in rats, which had not been observed in previous nonclinical studies. Dose levels in this study were 100 and 1000 mg/kg/day in males and 120 and 600 mg/kg/day in females. The observation consisted of mild to moderate vascular necrosis and vascular/perivascular inflammation in large pulmonary vessels in male rats. The finding was considered adverse and led to a NOAEL not being identified for males in the study. Following a recovery period of 6 weeks, minimal vascular/perivascular fibrosis with pigment-laden macrophages were noted in the lung of one recovery male. This finding was interpreted as an ongoing resolution of the vascular changes. There were no such findings in female rats or in dogs following chronic treatment.
The Information for healthcare professionals addresses the risk of infections, including pneumonia. Furthermore, the new nonclinical finding is adequately described in the Information for healthcare professionals and the RMP.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

The previously developed population PK model for pirtobrutinib was updated using pooled PK data from phase 1/2 study 18001 (data cutoff: 8 February 2023) and pivotal phase 3 study 20020 (data cutoff: 29 August 2023). The two-compartment model with linear clearance and four transit compartments for absorption described the pirtobrutinib PK of patients from study 20020 and study 18001 well. No dose adjustments are required based on any of the evaluated covariates.
Based On simulations, 97% of patients are predicted to exceed 90% inhibition of BTK and 66% of patients are predicted to achieve concentrations which exceed 96% inhibition of BTK at steady state at the proposed dose of 200 mg once daily (QD).

Whereas no relationship between pirtobrutinib exposure (C_{avg} and C_{min}) and objective response rate (ORR) was observed in CLL patients from pivotal phase 3 study 20020, higher pirtobrutinib trough exposure (C_{min}) was associated with longer progression-free survival (PFS).
No increased risk for neutrophil count decrease or alteration of systolic and diastolic blood pressure was associated with higher pirtobrutinib exposure. Increased pirtobrutinib C_{max} led to elevated haemoglobin levels.

5.2 Dose finding and dose recommendation

The applicant provided the following rationale for dose finding and dose recommendation for pirtobrutinib in CLL:

Pirtobrutinib's starting dose of 200 mg once daily (QD) is associated with meaningful benefits and an acceptable safety profile for patients with CLL.

The simulated popPK profiles over the studied clinical dose range (25 to 300 mg QD) based on the combined population from study 18001 and study 20020 were compared with the *in vitro* protein binding-adjusted IC_{50} for BTK. It was found that:

- At doses ≥100 mg QD, ≥80% of patients are predicted to achieve pirtobrutinib concentrations that exceed 90% inhibition of BTK at steady state.
- At the recommended commercial starting dose of 200 mg QD, 97% of patients are predicted to exceed 90% inhibition of BTK, and 66% of patients are predicted to achieve concentrations that exceed 96% inhibition of BTK at steady state.

Therefore, the proposed starting dose of 200 mg QD on the label allows patients to experience extensive and sustained BTK inhibition that is expected to yield treatment benefit.

Additionally, exposure-response analyses suggested that:

- A higher pirtobrutinib exposure (C_{min}) was found to be associated with longer PFS in CLL patients in phase 3 study 20020. Comparing patients at the 5th and 95th percentile of C_{min} in the PFS population, one-year survival was 28% for the 5th versus 63% for the 95th percentile. This translates to a hazard ratio of 2.8 (90% CI of 1.3 to 8.4) for patients at the 5th percentile of C_{min} compared to patients at the 95th percentile of C_{min} in the analysis population in study 20020 PFS.
- No increased risk for neutrophil count decrease, or alteration of systolic and diastolic blood pressure, once pirtobrutinib exposure increases.
- Increased pirtobrutinib exposure (C_{max}) is associated with an increase in haemoglobin level.

Thus, at the proposed starting dose of 200 mg QD, pirtobrutinib exposure did not negatively impact safety measures at the range of exposures in phase 3 CLL patients. Notably, CLL patients with a higher exposure tended to derive greater benefits compared to those with lower exposure. These benefits included a higher probability of PFS and an increase in haemoglobin levels.

Overall, the new data presented here from study 20020 suggests there is a positive exposure-response relationship for pirtobrutinib, i.e., higher exposure tends to bring more benefit to patients with CLL without increasing risk for the safety endpoints explored.

The applicant's rationale was accepted.

5.3 Efficacy

The efficacy of pirtobrutinib in 189 patients who had previously received at least two lines of therapy, including a BTK inhibitor, was investigated in the randomised, multicentre, international, open-label, actively controlled study 20020. Patients were randomised in a 1:1 ratio to receive either oral pirtobrutinib once daily at a dose of 200 mg until disease progression or unacceptable toxicity, or to the control arm, where they received one of the following two treatment options, as chosen by the study physician:

- Idelalisib plus rituximab (IR): Idelalisib 150 mg orally twice daily until disease progression or unacceptable toxicity, in combination with eight infusions of a rituximab product (375 mg/m² intravenously on day 1 of cycle 1, followed by 500 mg/m² every two weeks for four doses, and then every four weeks for three doses) in a 28-day cycle.
- Bendamustine plus rituximab (BR): Bendamustine 70 mg/m² intravenously (on days 1 and 2 of a 28-day cycle), in combination with a rituximab product (375 mg/m² intravenously on day 1 of cycle 1, followed by 500 mg/m² on day 1 of subsequent cycles) for up to six cycles.

Randomisation was stratified by 17p deletion status and prior treatment with venetoclax.

The study excluded patients with known or suspected Richter's transformation, active central nervous system (CNS) involvement by lymphoma, significant cardiovascular disease including uncontrolled or symptomatic arrhythmias, severe bleeding during prior treatment with a covalent BTKi, drug-induced pneumonitis, drug-induced liver injury, liver cirrhosis and/or extrahepatic obstructions, active infections (hepatitis B or C, CMV, HIV, or other clinically relevant infections), prior allogeneic or autologous stem cell transplantation or CAR-T therapy within the last 60 days, or vaccination with a live vaccine within the last 28 days.

Of the 189 patients, 98 were assigned to pirtobrutinib monotherapy, 64 received IR, and 27 received BR. On confirmation of disease progression, patients randomised to IR or BR had the option of switching to pirtobrutinib monotherapy (crossover). The median patient age was 67 years (range: 42 to 90 years), 69% were male, and 83% were white. The ECOG performance status at baseline was 0 or 1 in 95% of patients, and 50% of patients had RAI stage III or IV disease. A total of 46% (87 of 189 patients) had a 17p deletion and/or TP53 mutation, 72% (137 of 189 patients) had unmutated immunoglobulin heavy chain variable region gene (IGHV), and 45% (85 of 189) had a complex karyotype.
Patients had previously received a median of 3 lines of therapy (range: 2 to 13), with 71% having received at least 3 prior lines of therapy and 63% having previously received a BCL2 inhibitor. The most commonly used prior BTKi were ibrutinib (89%), acalabrutinib (16%), and zanubrutinib (7%). A total of 74% of patients had discontinued their last BTKi because of refractory disease or progression, 16% because of toxicity, and 10% for other or unknown reasons.

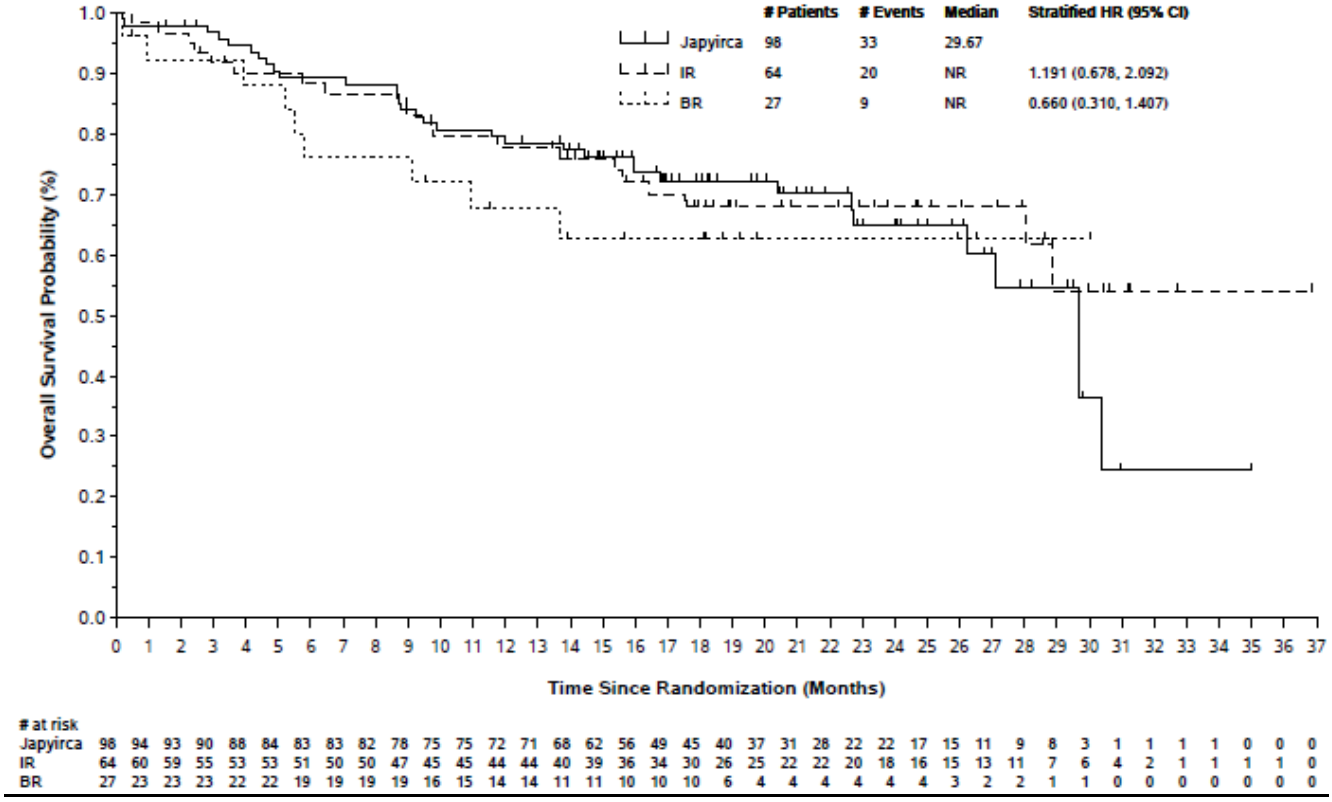
Efficacy was evaluated using the 2018 International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) guidelines. The primary endpoint was progression-free survival (PFS), as assessed by an independent review committee (IRC). PFS for the 189 patients who had previously received at least two lines of therapy, including a BTKi, after a median follow-up of 19.4 months (range: 0.03 to 33.3 months) for the pirtobrutinib arm and 17.7 months (range: 0.03 to 25.0 months) for the control arm, was improved in favour of the pirtobrutinib arm as follows:

- The hazard ratio (HR) for PFS, based on a stratified Cox proportional hazards model, was 0.45 (95% confidence interval [CI]: 0.31 to 0.65).
- Median PFS for the pirtobrutinib arm was 13.9 months (95% CI: 11.1 to 16.5), while the median PFS for the control arm was 8.3 months (95% CI: 5.8 to 9.0).

- 64 PFS events (65%) were observed in the pirtobrutinib arm, compared to 66 events (72%) in the control arm (IR or BR). Among these events, disease progression occurred in 53 patients (54%) in the pirtobrutinib arm and 54 patients (59%) in the control arm, while deaths as a result of PFS events were reported in 11 patients (11%) vs 12 patients (13%) in the control arm.

After a median observation period for overall survival (OS) of 20.5 months for the pirtobrutinib arm and 19.2 months for the control arm, 33 of the 189 patients (33.7%) in the pirtobrutinib arm and 29 patients (31.9%) in the control arm had died. The hazard ratio (HR) was 1.021 (95% CI: 0.618, 1.688), and the median OS was 29.7 months (95% CI: 26.3, not estimable [NE]) in the pirtobrutinib arm and was not reached in the control arm. The OS analysis may have been confounded by 41 out of 91 patients who crossed over from the control arm to pirtobrutinib. Additionally, Figure 1 illustrates the OS for both treatment options in the control arm, IR and BR separately.

Figure 1: Kaplan-Meier curve for OS in patients with CLL and prior treatment with at least 2 lines of therapy, including a BTKi (N=189) – study 20020, data cut-off August 2024



5.4 Safety

The initial safety analysis as of data cut-off (DCO) August 2023 reported fewer patients in study 20020 arm A (pirtobrutinib) as compared to arm B (IR/BR) with treatment-emergent adverse events (TEAEs) of any grade, grade 3/4, serious TEAEs, and TEAE leading to dose modification and treatment discontinuation. At the updated DCO in August 2024, there was a comparable proportion of patients with serious adverse events (SAEs) in arm A and arm B, and a higher proportion for pirtobrutinib vs BR (47.4% vs 37.5%), while the proportion for grade 3/4 TEAEs was comparable for pirtobrutinib vs BR (47.4% vs 53.1% as compared to 38.8% vs 53.1% at the initial analysis). Similarly, whereas TEAEs leading to dose modification and treatment discontinuation were still lower in arm A vs arm B overall, more patients in arm A vs BR reported AEs necessitating dose interruptions (50.9% vs 43.8% as compared to 35.3% vs 43.8% at the initial analysis) and treatment discontinuation (17.2% vs 9.4% as compared to 10.3% vs 9.4% at the initial analysis). This means that the better overall comparative safety profile of pirtobrutinib is primarily driven by the comparison with IR, which

has a safety profile known for an increased rate of serious and fatal toxicities. For this reason, IR is typically used only after prior covalent BTKi and BCL2i therapy, which both have better safety profiles than IR. This observation is supported by treatment-emergent infections, which are the most common all-grade and fatal TEAEs under pirtobrutinib treatment. While the difference between pirtobrutinib and IR in the proportion of patients suffering from all-grade infections is minor (64% vs 58%), it is relevant when compared to BR (64% vs 28%).

It is of further note that – as for total deaths in the updated OS analysis – the number of fatal (grade 5) AEs was numerically higher in arm A vs arm B (10.3% vs 9.2% as compared to 6.0% vs 9.2% at the initial analysis), although incidences of fatal AEs were similar across treatment arms. Infections accounted for the majority of this increase and the incidence of fatal TEAEs overall.

As of the updated DCO of August 2024, the most commonly reported AEs (in ≥ 10% of patients) of any grade by preferred term in arm A were pneumonia, anaemia, neutropenia, cough, diarrhoea, pyrexia, COVID-19, nausea, headache, fatigue, peripheral oedema, and upper respiratory tract infection.

Generally, lower or comparable proportions of patients experienced commonly reported treatment-emergent AEs in arm A compared to arm B, except for pneumonia, which was reported by a notably higher proportion of patients in arm A (any grade: 22.4% vs. 11.9%, and grade 3/4: 15.5% vs 8.3%). In many cases, however, the better comparative safety profile of pirtobrutinib was driven by the comparison with IR, which was more toxic than BR and was the comparator used in the majority (71%) of patients in the safety population of arm B.

No new safety signal has been reported for pirtobrutinib. The Information for healthcare professionals for Jaypirca® already included pertinent warnings for the known safety risks (infections, bleeding, cytopenia, atrial fibrillation / flutter, tumour lysis syndrome, and second primary malignancy).

5.5 Final clinical benefit risk assessment

Pivotal study 20020 was formally positive, showing a PFS benefit for the pirtobrutinib arm. Although the OS HR increased numerically between the primary and final analyses, with the OS HR point estimator exceeding 1, additional sensitivity analyses conducted by the applicant suggest that the post-progression crossover to pirtobrutinib in the control arm affected the OS result and contributed to the increased OS HR. Based on the available evidence, it is concluded that while study 20020 did not demonstrate any benefit to OS, the probability of a detriment to OS is low.

Study results from the 189 patients who had received at least two prior lines of therapy, including a BTKi, are important as the 3L+ CLL setting is associated with a poor prognosis and limited therapeutic options. IR, which was the therapy used in the majority of patients in control arm B, is one of these therapeutic options, but has significant toxicity. Pirtobrutinib showed a better safety profile than IR in registration study 20020.

Taking these two factors together, the benefit-risk balance for the approved indication was considered positive. However, because of the uncertainty regarding the OS results, the applicant was requested to include the OS Kaplan-Meier curves for all three treatments in the Information for healthcare professionals along with adequate information on the extent of crossover. In addition, five-year OS data will have be submitted with updated safety results by August 2028 as a post-approval requirement.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Jaypirca was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Jaypirca has authorised indications for a limited duration, see the section 'Indications and Usage".

JAYPIRCA®

Composition

Active substances

Pirtobrutinib

Excipients

Hypromellose acetate succinate, cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, magnesium stearate, silica colloidal hydrated
Hypromellose (E464), titanium dioxide (E171), triacetin, indigo carmine (E132)

Jaypirca 50 mg film-coated tablets

Each film coated tablet contains 38.3 mg of lactose (as monohydrate).
Each film coated tablet contains 0.7 mg of sodium (as croscarmellose sodium).

Jaypirca 100 mg film-coated tablets

Each film-coated tablet contains 76.5 mg of lactose (as monohydrate).
Each film coated tablet contains 1.4 mg of sodium (as croscarmellose sodium).

Pharmaceutical form and active substance quantity per unit

Film-coated tablets containing 50 mg resp. 100 mg of pirtobrutinib.

Jaypirca 50 mg film-coated tablets

Blue, 9 x 9 x 4 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 x 6 mm, round tablet debossed with “Lilly 100” on one side and “7026” on the other side.

Indications/Uses

Indication authorised for a limited duration

Jaypirca in monotherapy is indicated for treatment of adult patients with recurrent or refractory mantel cell lymphoma (MCL), who have received at least two lines of systemic treatments before, including an anti-CD20 antibody and a Bruton's tyrosine kinase (BTK) inhibitor, and when the patients are not suitable for a CAR-T therapy (see «clinical efficacy»).

This indication(s) has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

Non limited authorisation

Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have received at least two prior lines of therapy, including a BTK inhibitor (see «Clinical efficacy»).

Dosage/Administration

Usual dosage

The recommended dose is 200 mg pirtobrutinib once daily.
Treatment should be continued until disease progression or unacceptable toxicity.

Dose adjustment

Recommended dose modifications for Grade 3 or 4 adverse reactions are described in the table below.

Table 1. Recommended dose adjustments for specified adverse reactions

Specified adverse reaction[a]	Occurrence of the same specified adverse reaction requiring dose modification	Modification
• Grade 3 or 4 non-haematologic toxicity[b]	For the 1st time	Suspend Jaypirca until recovery to Grade 1 or baseline. Resume at original dose of 200 mg once daily.

Absolute neutrophil count < 1 to 0.5 x 10^9/L with fever and/or infection • Absolute neutrophil count < 0.5 x 10^9/L lasting 7 or more days • Platelet count < 50 to 25 x 10^9/L with bleeding • Platelet count < 25 x 10^9/L	For the 2nd time	Suspend Jaypirca until recovery to Grade 1 or baseline. Resume at reduced dose of 100 mg once daily.
	For the 3rd time	Suspend Jaypirca until recovery to Grade 1 or baseline. Resume at reduced dose of 50 mg once daily.
	For the 4th time	Discontinue Jaypirca.

[a] Dose modification is not recommended for asymptomatic lymphocytosis. Asymptomatic lipase increase may not necessarily warrant dose modification.
[b] Evaluate the benefit-risk before resuming treatment at the same dose for a Grade 4 non-hematological toxicity.

Severity grade assignment based on *National Cancer Institute Common Terminology Criteria for Adverse Events* (NCI CTCAE)

Dosage Modifications for Concomitant Use with 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 dosage of Jaypirca is 200 mg once daily, increase the dose to 300 mg. If the current dosage is 50 mg or 100 mg once daily, increase the dose by 50 mg.

Dosage Modifications for Concomitant Use with Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors with Jaypirca (see “Interactions” and “Pharmacokinetics”). If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the Jaypirca dose by 50 mg. If the current dosage is 50 mg once daily, interrupt Jaypirca treatment for the duration of strong CYP3A inhibitor use. Five half-lives after discontinuation of a strong CYP3A inhibitor, resume the Jaypirca dose that was taken prior to initiating the strong CYP3A inhibitor.

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. If vomiting occurs, do not take an additional dose, continue with the next scheduled dose.

Elderly

No dose adjustment is required based on age (see section “Pharmacokinetics” and “Undesirable effects”).

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 (see section “Pharmacokinetics”). No dosage adjustment of Jaypirca is recommended in patients with mild to moderate renal impairment (eGFR 30-89 mL/min).
There are no data in patients on dialysis (see section “Pharmacokinetics”).

Hepatic impairment

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

Pediatric population

Jaypirca is not approved for use in pediatric population.

Mode of administration

For oral use.
The tablet should be swallowed whole 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition”.

Warnings and precautions

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients treated with Jaypirca. In the clinical trials, Grade 3 or higher infections occurred in 25.4% of 704 patients, most commonly pneumonia (8.9%), with fatal infections occurring in 5.0% of patients. Sepsis occurred in 5.8% of patients and febrile neutropenia in 3.8%. Opportunistic infections after treatment with Jaypirca have included, but are not limited to, *Pneumocystis jirovecii* pneumonia and fungal infection.

Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients who are at increased risk for infections, including opportunistic infections. Monitor patients for signs and symptoms

of infection, evaluate promptly, and treat appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca *(*see “Dosage/Administration”).

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.

Hemorrhage

Fatal and serious hemorrhage has occurred with Jaypirca. Major hemorrhage (defined as Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.1% of 704 patients treated with Jaypirca, including gastrointestinal hemorrhage; fatal hemorrhage occurred in 0.3% of patients. Bleeding of any grade, excluding bruising and petechiae, occurred in 19.2% of patients.

Major hemorrhage occurred in 2.4% of patients taking Jaypirca without antithrombotic agents and 0.7% of patients taking Jaypirca with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with Jaypirca. Monitor patients for signs of bleeding. Based on severity of bleeding, reduce dose, temporarily withhold, or permanently discontinue Jaypirca (see Dosage and Administration).

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

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (23.2%), anemia (10.4%), and thrombocytopenia (8.9%) have developed in patients treated with Jaypirca.

Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca *(see “Dosage/Administration").*

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation and atrial flutter were reported in recipients of Jaypirca. Atrial fibrillation or flutter were reported in 3.4% of patients, with Grade 3 or 4 atrial fibrillation or flutter reported in 1.6% of 704 patients in the clinical trials. Patients with cardiac risk factors, such as hypertension, or previous arrhythmias may be at increased risk.

Monitor for signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea) and manage appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca *(see “Dosage/Administration”)*.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, developed in 8.7% of 704 patients treated with Jaypirca monotherapy. The most frequent malignancy was non-melanoma skin cancer, reported in 4.4% of 704 patients. Other second primary malignancies included solid tumors (including genitourinary and breast cancers) and melanoma. Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Hepatotoxicity including drug-induced liver injury (DILI)

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI) occurred in patients treated with Bruton tyrosine kinase inhibitors, including Jaypirca. Before the initiation and during treatment with Jaypirca, the bilirubin and transaminase values must be monitored. Patients who develop abnormal liver function values after use of Jaypirca should be monitored more frequently for abnormalities in liver function tests and clinical signs of hepatotoxicity. If DILI is suspected, the treatment with Jaypirca must be withheld. After DILI is confirmed, Jaypirca must be discontinued.

Embryo-Fetal Toxicity

Jaypirca can cause fetal harm when administered to a pregnant woman (see “Pregnancy, lactation”).

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’.

Interactions

Effects of pirtobrutinib on other medicinal products

Cytochrome P450 (CYP)-enzymes: *In Vitro* pirtobrutinib inhibits CYP2C8, CYP2C9, CYP3A, CYP1A2, CYP2B6, CYP2C19, and CYP2D6. *In Vitro* pirtobrutinib induces CYP3A4, CYP3A5, CYP2B6, and CYP2C19.

Transporter systems: In vitro pirtobrutinib inhibits P-gp and BCRP, but not OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

Table 2. Clinical Effects of pirtobrutinib on other medicinal products

Concomitant medication (enzyme or transporter)	Conmed dosing regimen	Pirtobrutinib dose	GMR [a] (90 % CI [b])		Posology recommendation for concominant medication
			C_{max}	$AUC_{0\text{-}inf}$	
Midazolam (CYP3A substrate)	Midazolam 250 µg IV single dose	200 mg QD	0.99 (0.834, 1.18)	1.12 (1.04, 1.21)	For substrates where minimal concentration changes may increase the risk of adverse reactions, follow recommendations for coadministration with inhibitors of CYP2C8, CYP2C19, CYP3A, P-gp, or BCRP provided in their approved product labeling
	Midazolam 500 µg oral single dose	200 mg QD	1.58 (1.40, 1.78)	1.70 (1.55, 1.86)	
Caffeine (CYP1A2 substrate)	Caffeine 200 mg single dose	200 mg QD	0.99 (0.93, 1.05)	0.94 (0.91, 0.98)	
S-Warfarin (CYP2C9 substrate)	Warfarin 10 mg single dose	200 mg QD	1.02 (0.974, 1.06)	1.11 (1.08, 1.14)	
Omeprazole (CYP2C19 substrate)	Omeprazole 40 mg single dose	200 mg QD	1.49 (1.31, 1.70)	1.56 (1.35, 1.80)	
Repaglinide (CYP2C8 substrate)	Repaglinide 0.5 mg single dose	200 mg QD	1.98 (1.62, 2.43)	2.30 (1.86, 2.84)	
Digoxin (P-gp substrate)	Digoxin 0.25 mg BID / QD [d]	200 mg single dose	1.51 (1.32, 1.73)	1.17 (1.11, 1.23) [c]	
		200 mg QD	1.55 (1.35, 1.78)	1.35 (1.29, 1.42) [c]	
Rosuvastatin (BCRP substrate)	Rosuvastatin 20 mg single dose	200 mg single dose	2.43 (2.18, 2.71)	2.18 (2.00, 2.37)	
		200 mg QD	2.46 (2.20, 2.75)	2.40 (2.21, 2.62)	

[a] GMR = Geometric Mean Ratio defined by exposure (maximal concentration or area under the curve) of concomitant medication when given with pirtobrutinib dividing exposure of the concomitant medication without pirtobrutinib

[b] CI = Confidence Interval
[c] AUC_{tau}
[d] BID (twice daily) on Day 1, QD (once daily) thereafter

Effects of other medicinal products on pirtobrutinib

Metabolising enzymes: *In Vitro* pirtobrutinib is a substrate of CYP3A4, UGT1A8, and UGT1A9.
Transporter systems: *in Vitro* pirtobrutinib is a substrate of P-gp and BCRP, but not of OCT1, OATP1B1, OATP1B3 or BSEP. Pirtobrutinib is not a substrate of hepatic transporters.

Table 3. Clinical effects of other medicinal products on pirtobrutinib

Concomitant medication (enzyme or transporter)	Conmed dosing regimen	Pirtobrutinib dose	GMR [a] (90% CI [b])		Posology recommendation for pirtobrutinib
			C_{max}	AUC_{0-inf}	
Itraconzaole (Strong CYP3A inhibitor and P-gp Inhibitor)	200 mg itraconazole BID (twice daily) for 1 day then QD (once daily) for 10 days	200 mg single dose	1.04 (0.95, 1.13)	1.49 (1.40, 1.58)	Avoid concomitant use of strong CYP3A inhibitors, If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose by 50 mg. If the current dosage is 50 mg once daily, interrupt treatment for the duration of strong CYP3A inhibitor use. (see section “Dossage/Administration”) No dose adjustment necessary with P-gp inhibitors (see also results after a single dose of rifampicin).
Verapamil [c] (Moderate CYP3A Inhibitor)	80 mg three times daily	200 mg QD	1.21 (1.20, 1.22)	1.30 (1.29, 1.32)[d]	No dose adjustment necessary with

Diltiazem [c] (Moderate CYP3A inhibitor)	60 mg three times daily	200 mg QD	1.14 (1.13, 1.14)	1.20 (1.19, 1.21)[d]	moderate CYP3A inhibitors.
Rifampin (OATP1B and P-gp Inhibitor and Strong CYP3A Inducer)	600 mg rifampin QD for 16 days (Days 8 to 23)	200 mg single dose Day 8	0.93 (0.87, 1.0)	0.97 (0.94, 1.00)[e]	No dose adjustment necessary with OATP1B and P-gp inhibitors
		200 mg single dose Day 17	0.58 (0.54, 0.62)	0.29 (0.27, 0.32)	Avoid concomitant used with strong CYP3A inducers (see section “Dosage/Administration”)
Efavirenz[c] (Moderate CYP3A Inducer)	600 mg QD	200 mg QD	0.67 (0.65, 0.69)	0.51 (0.48 , 0.54)[d]	If concomitant use with moderate CYP3A inducers is unavoidable and the current dosage is 200 mg once daily, increase the dose to 300 mg. If the current dosage is 50 mg or 100 mg once daily, increase the dose by 50 mg (see section “Dosage/Administration”).
Bosentan [c] (Moderate CYP3A Inducer)	125 mg BID	200 mg QD	0.80 (0.79, 0.81)	0.73 (0.72, 0.75)[d]	
Omeprazole (Gastric Acid Reducing Agent)	40 mg QD	200 mg single dose	1.01 (0.86, 1.18)	1.11 (1.02, 1.22)	No dose adjustment with gastric acid reducing agents.

[a] GMR = Geometric Mean Ratio defined by exposure (maximal concentration or area under the curve) of pirtobrutinib when given with a concomitant medication dividing exposure of pirtobrutinib without the concomitant medication
[b] CI = Confidence Interval
[c] predicted interaction according to PBPK modeling
[d] GMR of AUC_{tau}
[e] GMR of AUC_{0-24h}

Pregnancy, lactation

Contraception

Women of childbearing potential have to use a reliable contraception during treatment and for at least 1 weeks after the last dose of pirtobrutinib.

Pregnancy

There are no available data on Jaypirca use in pregnant women. Animal studies have shown reproduction toxicity (see section “Preclinical Data”). Advise pregnant women of the potential risk to a fetus. Jaypirca should not be used during pregnancy.

Lactation

There are no data on the presence of Jaypirca in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with Jaypirca and for one week after the last dose.

Fertility

There is no clinical data on the effects of Jaypirca on the fertility in humans. Fertility studies in animals have not been conducted. In toxicity studies with repeated dosing with a duration of up to 3 months, pirtobrutinib has not had effects on male or female reproduction organs.

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. Adverse events occurred during therapy with Jaypirca, such as altered vision, cardiac arrhythmias, nausea, fatigue, and dizziness, which can impair the ability to drive and operate machines.

Undesirable effects

Summary of the safety profile

The summary of the safety profile and Table 4 lists the adverse effects associated with Jaypirca used as a monotherapy from clinical study data. The adverse effects are based on pooled data from 704 patients treated with Jaypirca monotherapy 200 mg QD in clinical studies.

Patients were treated for MCL, chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and other non-Hodgkin lymphoma (NHL).

The most common adverse effects of any grade (≥15%), were bleeding (34.7%), neutropenia (27.1%), fatigue (26.1%), diarrhea (23.2%), anaemia (18.8%), rash (17.9%), contusion (17.2%), oedema (16.2%), nausea (16.1%) and thrombocytopenia (15.5%). Grade 3 or greater laboratory abnormalities occurring in ≥5% of patients were lymphocyte count decreased (10.6%) and lipase increased (7.2%).

Serious adverse effects occurred in 25.3% of patients who received Jaypirca. Serious adverse effects that occurred in ≥2% of patients were pneumonia (8.1%), sepsis (4.7%), neutropenia (3.1%), second primary malignancies (2.7%), bleeding (2.6%) and anaemia (2.1%).

Fatal adverse effects occurred in 2.3% of patients, most commonly due to infections (1.4%) including pneumonia (0.4%) and sepsis (1.0%).

Adverse effects led to dosage reductions in 4.5%, treatment interruption in 27.7% and permanent discontinuation of Jaypirca in 5.8% of patients. Adverse effects leading to dosage modification in >5% of patients was neutropenia.

Tabular list of side effects

Side effects in patients who have been treated with Jaypirca for B-cell-malignancies, are listed below by system organ class and incidence. The incidences are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10‘000, <1/1000), very rare“ (<1/10‘000), unknown (can't be estimated based on available data). Within each group of incidence the undesirable reactions are presented in order of decreasing severity.

Table 4: Adverse effects of patients treated with Jaypirca monotherapy[a] at 200 mg QD

System organ class (MedDRA)	**Adverse effects**	**Frequency category (%) (All grades)** N=704	**Grade ≥3[a] (%)**
Blood and lymphatic system disorders	Neutropenia[b]	Very common (27.1)	23.2
	Anaemia[b]	Very common (18.8)	10.4
	Thrombocytopenia[b]	Very common 15.5	8.9
	Lymphocytosis[b]	Common	4.0
	Lymphocyte count decreased	Very common 30.3	10.6
Eye disorders	Vision changes[c]	Common	0.4
Cardiac disorders	Atrial fibrillation/Atrial flutter	Common	1.6
Gastrointestinal disorders	Diarrhea	Very common 23.2	1.0
	Nausea	Very common 16.1	0.3
	Abdominal pain	Very common 10.5	0.9
Hepato biliary disorders	AST increased	Very common 18.0	0.9
	ALT increased	Very common 23.4	2.0
	Lipase increased	Very common 18.7	7.2
	Fatigue	Very common	1.8

General disorders and administration site conditions		26.1	
	Pyrexia	Very common 14.3	1.0
	Oedema[c]	Very common 16.2	0.7
Infections and infestations	Pneumonia	Very common 13.2	8.9
	Upper respiratory tract infection	Common	0.1
	Urinary tract infection	Common	1.0
	Sepsis[c]	Common	5.4
Injury, poisoning, and procedural complications	Contusion	Very common 17.2	0.1
Musculoskeletal and connective tissue disorders	Arthralgia	Very common 14.2	1.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Secondary primary malignancies[c]	Common	3.1
Nervous system disorders	Headache	Very common 12.1	0.7
	Peripheral Neuropathy[c]	Very Common 13.6	1.6
	Dizziness	Common	0.0
Renal and urinary disorders	Hematuria	Common	0.0
	Blood creatinine increased	Very common 23.1	0.5
Respiratory, thoracic, and mediastinal disorders	Epistaxis	Common	0.0
Skin and subcutaneous tissue disorders	Rash[b]	Very common 17.9	1.1
	Petechiae	Common	0.0
Vascular disorders	Haematoma	Common	0.1
	Bleeding[C]	Very common 34.7	2.8
Investigations	Calcium decreased	Very Common 30.4	1.3
	Potassium decreased	Very common 15.4	1.9
	Sodium decreased	Very common 27.3	0.7
	Alkaline phosphatase increased	Very common 16.1	0.3
	Potassium increased	Very common 14.1	1.4
Metabolism and nutrition disorders	Tumour lysis syndrome	Uncommon	0.7

[a] Severity grade assignment based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
[b] Consolidated term.
[c] Each term listed includes other related terms.

Description of specific adverse reactions and additional information

Lymphocytosis

Upon initiation of Jaypirca, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count increased ≥50% from baseline and a post-baseline value ≥5,000/µL) occurred in 45% of the pooled safety popuation who have received 200 mg daily dose. The median time to onset of lymphocytosis was 1.1 weeks, with 75% of cases occurring within 1.3 weeks, and the median duration was 15.0 weeks.

Specific Populations

Elderly

In the pooled safety population in patients with hematologic malignancies, 467 (66.3%) were 65 years of age and older, while 181 (25.7%) were 75 years of age and older. Patients aged 65 years and older experienced higher rates of Grade 3 and higher adverse reactions and serious adverse reactions compared to patients who were less than 65 years of age.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, use supportive therapy. There is no known antidote for pirtobrutinib overdose.

Properties/Effects

ATC code

L01EL05

Mechanism of action

Pirtobrutinib is a reversible noncovalent inhibitor of Bruton's tyrosine kinase (BTK). BTK is a signaling protein of the B-cell antigen receptor and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Pirtobrutinib binds to wild type and BTK C481 mutants, leading to inhibition of BTK kinase activity. In nonclinical studies, pirtobrutinib inhibited BTK-mediated B-cell CD69 expression and inhibited malignant B-cell proliferation. Pirtobrutinib showed dose-dependent tumor growth inhibition and induced tumor regression in BTK wild-type and BTK C481S-mutant mouse xenograft models.

Pharmacodynamics

At the recommended dosage of 200 mg once daily, pirtobrutinib trough concentrations exceeded the BTK IC96. BTK occupancy is maintained throughout the dosing interval, regardless of the intrinsic rate of BTK turnover.

Cardiac Electrophysiology

The effect of a single 900 mg dose of pirtobrutinib on the 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 QTcF interval (that is, >10 ms), and there was no relationship between pirtobrutinib exposure and change in QTc interval.

Clinical efficacy

Mantle Cell Lymphoma

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

The median age was 71 years (range: 46 to 88 years); 79% were male; 78% were White, 14% Asian, 1.7% Black or African American. Seventy-eight percent of patients had the classic/leukemic variant of MCL, 12% had pleomorphic MCL, and 11% had blastoid MCL. The simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI) score was low in 15%, intermediate in 59%, and high in 26% of patients. Patients received a median number of 3 prior lines of therapy (range: 1 to 9) with 93% having received 2 or more prior lines. All received 1 or more prior lines of therapy containing a BTK inhibitor; other prior therapies included chemoimmunotherapy in 88%, HSCT in 20%, lenalidomide in 18%, and CAR-T therapy in 9%. The most common prior BTK inhibitors received were ibrutinib (67%), acalabrutinib (30%), and zanubrutinib (8%). 83% of patients discontinued the last BTK inhibitor for refractory or progressive disease, 10% discontinued for toxicity, and 5% discontinued for other reasons. Efficacy was based on overall response rate (ORR) and duration of response (DOR), as assessed by an independent review committee (IRC) using 2014 Lugano criteria.

In 120 efficacy eligible patients, the objective response rate (ORR) was 50 %, (95% CI: 41, 59), including 13 % with complete response (CR).
Time to response was 1.8 months (95% CI: 0.8, 4.2). Duration of response was 8.3 months (95% CI: 5.7, NE).

Additionally, the Kaplan-Meier estimate for the DOR rate at 6 months was 65.3% (95% CI: 49.8, 77.1).

Chronic Lymphocytic Leukaemia

The efficacy of Jaypirca in 189 patients who received at least two prior lines of therapy including a BTK-inhibitor was evaluated in a randomised, multicentre, international, open-label, actively-controlled trial (BRUIN CLL-321, Study 20020). 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 in the control arm with one of the following 2 treatment options as per 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.

The trial excluded patients with known or suspected Richter's transformation, active central nervous system (CNS) involvement by lymphoma, significant cardiovascular disease including uncontrolled or symptomatic arrhythmias, major bleeding on a prior covalent BTK inhibitor, drug-induced pneumonitis, drug-induced liver injury, liver cirrhosis and/or extrahepatic obstructions, active infections (hepatitis B or C, CMV, HIV or other clinically significant infections), prior allogeneic or autologous SCT or CAR-T therapy within the past 60 days, or vaccination with a live vaccine within prior 28 days.

Randomisation was stratified by 17p deletion status (yes/no) and receipt of prior venetoclax treatment (yes/no).
Of the 189 patients, 98 were assigned to Jaypirca monotherapy, 64 to IR and 27 to BR. After confirmed disease progression, patients randomised to IR or BR had the option to cross over to Jaypirca monotherapy. The median age was 67 years (range: 42 to 90 years), 69% were male and 83% were White. Baseline ECOG performance status was 0 or 1 in 95% of patients and 50% of patients had Rai stage III or IV disease. 46% (87 of 189 patients) had 17p deletion and/or TP53 mutation, 72% (137 of 189 patients) had unmutated IGHV, and 45% (85 of 189 patients) had complex karyotype.

Patients received a median number of 3 prior lines of therapy (range: 2 to 13) with 71% having at least 3 prior therapies and 63% having had prior BCL2-inhibitor therapy. The most common prior BTK inhibitors received were ibrutinib (89%), acalabrutinib (16%), and zanubrutinib (7%). 74% of patients discontinued the most recent BTK inhibitor for refractory or progressive disease, 16% discontinued for toxicity, and 10% discontinued for other/missing reasons.

Efficacy was based on PFS as assessed by an IRC (independent review committee). Efficacy results for the 189 patients who received at least two prior therapy lines including a BTK inhibitor are presented in Table 5. after 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 25.0 months) for the control arm.

Table 5: Efficacy Results per IRC in Patients with CLL Previously Treated with at Least Two Prior Lines of Therapy, including a BTK Inhibitor – Study 20020, data cut August 2024.

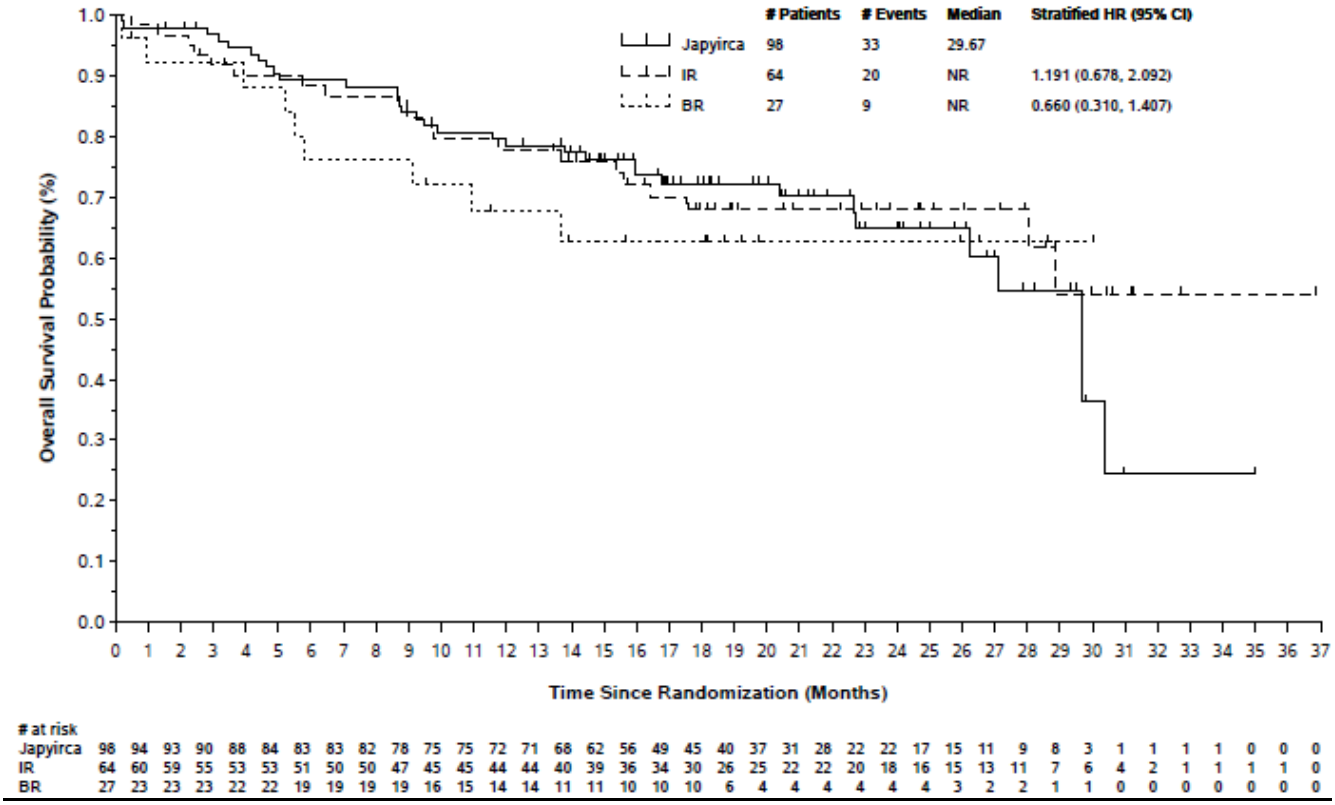
	Pirtobrutinib 200 mg once daily (N = 98)	**Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab (N = 91)**
Progression-free Survival[a]		
Number of Events, n	64 (65 %)	66 (72 %)
Disease Progression	53 (54 %)	54 (59 %)
Death	11 (11 %)	12 (13 %)
Median PFS (95% CI), months [b]	13.9 (11.1, 16.5)	8.3 (5.8, 9.0)
HR (95% CI) [c]	0.45 (0.31, 0.65)	

CI, confidence interval; HR, hazard ratio.
[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.

Of the 189 patients and with a median overall survival (OS) follow-up time of 20.5 months for pirtobrutinib and 19.2 months in the control arm, 33 patients (33.7 %) in the pirtobrutinib arm and 29 patients (31.9 %) in the control arm died. Median OS was 29.7 months (95 % CI: 26.3, NE) in the pirtobrutinib arm and not reached in the control arm. The HR was 1.021 (95% CI: 0.618, 1.688).

OS analysis may be confounded by 41 out of 91 patients who switched from the control arm to pirtobrutinib (crossed over). In addition, Figure 1 presents OS separately for both treatment options of the control arm (IR and BR).

Figure 1: Kaplan-Meier Curve of OS in Patients with CLL Previously Treated with at least Two Prior Lines of Therapy, including a BTK Inhibitor - Study 20020, data cut August 2024



Pharmacokinetics

The pharmacokinetics of pirtobrutinib were characterized in healthy subjects and in patients with cancer. Pirtobrutinib exposure (AUC) and C_{max} increases proportionally following single oral doses ranging from 300 mg to 800 mg (1.5 to 4 times the approved recommended dosage) and once daily doses ranging from 25 – 300 mg (0.125 to 1.5 times the recommended dosage). Steady state was achieved within 5 days of once daily dosing, and the mean (CV%) accumulation ratio was 1.63 (26.7%) based on AUC after administration of 200 mg dosages. Following administration of the recommended dosage, the geometric mean (CV%) steady-state AUC and Cmax of pirtobrutinib were 92600 h*ng/mL 39%) and 6500 ng/mL (25%), respectively. The geometric mean (CV%) AUC_{0-24} and Cmax of pirtobrutinib on Cycle 1 Day 8 were 81800 h*ng/mL (66.6%) and 3670 ng/mL (89.5%), respectively.

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.

Effect of food

A high-fat, high-calorie meal administered to healthy subjects decreased pirtobrutinib Cmax by 23% and delayed T_{max} by 1 hour. There was no effect on pirtobrutinib AUC.

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. Mean blood-to-plasma ratio is 0.79.

Metabolism

Pirtobrutinib is primarily metabolized by CYP3A4 and direct glucuronidation by UGT1A8 and UGT1A9, in vitro.

Elimination

The mean apparent clearance of pirtobrutinib is 2.05 L/h with an effective half life of approximately 19 hours. Following a single radiolabeled dose of pirtobrutinib 200 mg to healthy subjects, 37% of the dose was recovered in feces (18% unchanged) and 57% in urine (10% unchanged).

Kinetics in specific patient groups

Age, gender and body weight

Based on a population pharmacokinetic analysis in patients with cancer, age (range 22-95 years), sex (523 males and 257 females), and body weight (range 35.7-152 kg), race (White 84%, Asian 8%) had no clinically meaningful effect on the exposure of pirtobrutinib.

The effect of other races/ethnicities on the pharmacokinetics of pirtobrutinib is unknown.

Hepatic impairment

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

In a population pharmacocinetic analysis in patients with cancer, there were no clinically significant differences in the pharmacokinetics of pirtobrutinib in patients with mild (total bilirubin = upper limit of normal (ULN) and aspartate aminotransferase (AST) >ULN or total bilirubin >1 to 1.5 × ULN and any AST), moderate (total bilirubin >1.5 to 3 × ULN and any AST), or severe (total bilirubin >3 × ULN and any AST) hepatic impairment.

Renal impairment

Following a single 200 mg oral dose, the AUC of pirtobrutinib in subjects with severe renal impairment (eGFR 15-29 mL/min) increased by 62% and mean unbound AUC increased by 68% compared to healthy subjects with normal renal function. There were no clinically significant differences in the pharmacokinetics of pirtobrutinib in subjects with mild (eGFR 60-89 mL/min) or moderate renal impairment (eGFR 30-59 mL/min). The effect of renal impairment requiring dialysis on the pharmacokinetics of pirtobrutinib is unknown.

Preclinical data

Safety pharmacology / toxcicity after repeated dose

Repeat-dose studies were conducted in rats and dogs to characterize toxicity. Important effects in both rats and dog consisted of decreased size, weight, or cellularity of lymphoid organs and decreases in B lymphocytes and other markers of immune system function.Minimal to mild corneal lesions were observed only in dogs. 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.

Carcinogenesis

Carcinogenicity studies have not been conducted with pirtobrutinib.

Genotoxicity

Pirtobrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay. Pirtobrutinib was aneugenic in *in vitro* micronucleus assays using human peripheral blood lymphocytes. Pirtobrutinib had no effect in an *in vivo* rat bone marrow micronucleus assay.

Reproductive toxicity

In an animal reproduction study, administration of pirtobrutinib to pregnant rats during organogenesis resulted in adverse developmental outcomes, including structural abnormalities, altered fetal growth, and embyro-fetal mortality at maternal exosures approximately 3-times those in patients at the recommended daily dose of 200 mg.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging .
Keep out of the reach of children.

Authorisation number

68733 (Swissmedic).

Packs

Jaypirca 50 mg tablets in Blister: 28 (A)

Jaypirca 50 mg tablets in bottle: 30 (A)

Jaypirca 100 mg tablets in Blister: 28, 56 (A)

Jaypirca 100 mg tablets in bottle: 30, 60 (A)

Marketing authorisation holder

Eli Lilly (Suisse) SA, 1214 Vernier/Genève.

Date of revision of the text

July 2025