swissmedic

Date: 13 February 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Jaypirca

International non-proprietary name: pirtobrutinib

Pharmaceutical form: film-coated tablet

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: temporary authorisation in accordance with Art. 9a TPA approved on 30.11.2023

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

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
AE	Adverse event
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
BTK	Bruton's tyrosine kinase
CI	Confidence interval
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MCL	Mantle cell lymphoma
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
R/R	Relapsed/refractory
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)

New active substance status
The applicant requested new active substance status for pirtobrutinib in the above-mentioned medicinal product.

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

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Jaypirca is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least 2 lines of systemic therapy, including a BTK inhibitor, and when CAR T is not a treatment option.

2.2.2 Approved indication

Jaypirca as monotherapy is indicated for treatment of adult patients with recurrent or refractory mantel cell lymphoma (MCL), who have received at least 2 prior lines of systemic treatment, including an anti-CD20 antibody and a Bruton's tyrosine kinase (BTK) inhibitor, and if the patients are not suitable for CAR T-cell therapy (see "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
200 mg orally once daily.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	24 May 2023
Formal control completed	31 May 2023
Preliminary decision	8 August 2023
Response to preliminary decision	21 September 2023
Labelling corrections	17 October 2023
Response to labelling corrections	31 October 2023
Labelling corrections	8 November 2023

Response to labelling corrections	14 November 2023
Final decision	30 November 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the U.S. Food and Drug Administration (FDA). This SwissPAR relates to the publicly available assessment report for Jaypirca, film-coated tablets (NDA 216059), issued by FDA.

3 Medical context

Mantle cell lymphoma (MCL) is an incurable disease and prognosis after treatment with chemoimmunotherapy and BTK-inhibition is very poor, with a high risk of death in the short term. Available treatment options for third-line treatment of MCL are limited. Recently, CD19-directed CAR T-cell therapy has been approved for MCL after treatment with a BTK-inhibitor, with improved ORR (84%) and prolonged OS (median 47.4 months) compared with historical data. The safety profile is, however, associated with significant toxicity, including cytokine release syndrome (CRS), CAR T-cell-associated neurotoxicity, and haematological toxicity. Available treatment options for third-line treatment of patients with MCL who are not candidates for CD19-directed CAR T-cell therapy are limited and outcomes are unsatisfactory. Accordingly, there is an unmet medical need in this indication.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the U.S. Food and Drug Administration (FDA). The SwissPAR relating to quality aspects refers to the publicly available assessment report for Jaypirca, film-coated tablets (NDA 216059), issued by FDA.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the U.S. Food and Drug Administration (FDA). The nonclinical aspects in this SwissPAR refer to the publicly available assessment report for Jaypirca, film-coated tablets (NDA 216059).

6 Clinical aspects

6.1 Clinical and clinical pharmacology aspects

The evaluation of the clinical and clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment report and corresponding product information from FDA were used as a basis for the clinical and clinical pharmacology evaluation. The current SwissPAR relating to clinical aspects refers to the publicly available FDA assessment report.

The submitted indication differed from the indication approved by the FDA. Therefore, the assessment focused on the included patient population and efficacy of the ongoing uncontrolled study LOXO-BTK 18001 (BRUIN) in patients with relapsed/refractory (R/R) MCL. The MCL efficacy population consisted of 120 patients treated with the 200 mg once daily dosage throughout treatment (or whose dose was increased only after disease progression or permanent censoring). The median age of this population was 71 years. The median number of lines of prior systemic therapy was 3. Only 7.5% of patients received 1 line of prior therapy and the majority received ≥ 2 lines of prior therapies. All patients had received in minimum 1 prior BTK inhibitor. In total 95.8% of all patients had received prior treatment with an anti-CD20 antibody, which is recommended as part of upfront therapy for MCL. The characteristics of prior systemic treatment support the indication for patients with at least 2 prior lines of systemic therapy, including a BTK inhibitor and an anti-CD20 antibody. Only 9.2% of patients had received prior CAR T-cell therapy.

For further details concerning clinical pharmacology, dosing recommendations, efficacy, and safety, see the attached information for healthcare professionals.

The submitted single arm study BRUIN with overall response rate (ORR) as primary endpoint does not fulfil the criteria for a confirmatory study according to ICH-E9. In addition, ORR is not validated as surrogate marker for overall survival (OS). Furthermore, evaluation of safety in patients with R/R MCL was limited due to the small patient population. Therefore, the currently available clinical data for pirtobrutinib are not sufficient for authorisation without special conditions.

However, for patients who are not eligible for CAR T cells or who progress after CAR T-cell therapy, the results of the BRUIN study are encouraging, and a major therapeutic benefit could be expected from use of pirtobrutinib in patients with R/R MCL after ≥ 2 prior systemic therapies, including an anti-CD20 antibody and a BTK inhibitor. Therefore, the requested temporary authorisation can be granted.

In order to further confirm the currently available results, the applicant will submit updated efficacy and safety data from the ongoing pivotal phase 1/2 study LOXO-BTK 18001 (BRUIN) and the ongoing confirmatory phase 3 study (LOXO-BTK-20019 /BRUIN MCL-321) as well as the two post-marketing studies on long-term safety and on the risk of secondary primary malignancies.

7 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.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Jaypirca, film-coated tablets, 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 been authorised temporarily, see “Indications/Uses” section.

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

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/these indication(s) has/have 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.

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] • Grade 3 neutropenia with fever and/or infection • Grade 4 neutropenia lasting ≥ 7 days • Grade 3 thrombocytopenia with bleeding • Grade 4 thrombocytopenia	For the 1st time	Suspend Jaypirca until recovery to Grade 1 or baseline. Resume at original dose of 200 mg once daily.
	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).

Children and adolescents

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

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 trial, Grade 3 or higher infections occurred in 17% of 583 patients, most commonly pneumonia (9%), with fatal infections occurring in 4.1% of patients. Sepsis occurred in 4.5% of patients and febrile neutropenia in 2.9%. Opportunistic infections after treatment with Jaypirca have included, but are not limited to, *Pneumocystis jirovecii* pneumonia and fungal infection.

Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients who are at increased risk for infections, including opportunistic infections. Monitor patients for signs and symptoms of infection, evaluate promptly, and treat appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca *(*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 2.4% of 583 patients treated with Jaypirca, including gastrointestinal hemorrhage; fatal hemorrhage occurred in 0.2% of patients. Bleeding of any grade, excluding bruising and petechiae, occurred in 14% of patients.

Major hemorrhage occurred in 1.7% of patients taking Jaypirca without antithrombotic agents and 0.7% of patients taking Jaypirca with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with Jaypirca. Monitor patients for signs of bleeding. Based on severity of bleeding, reduce dose, temporarily withhold, or permanently discontinue Jaypirca (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 (24%), anemia (11%), and thrombocytopenia (11%) have developed in patients treated with Jaypirca. In the clinical trial, Grade 4 neutropenia developed in 13% of patients and Grade 4 thrombocytopenia developed in 5% of patients.

Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca *(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 2.7% of patients, with Grade 3 or 4 atrial fibrillation or flutter reported in 1.0% of 583 patients in the clinical trial. Patients with cardiac risk factors, such as hypertension, or previous arrhythmias may be at increased risk.

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

Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, developed in 6% of 583 patients treated with Jaypirca monotherapy. The most frequent malignancy was non-melanoma skin cancer, reported

in 3.8% of 583 patients. Other second primary malignancies included solid tumors (including genitourinary and breast cancers) and melanoma. Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Embryo-Fetal Toxicity

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
	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	Warfarin 10 mg single dose	200 mg QD	1.02	1.11 (1.08, 1.14)	

(CYP2C9 substrate)			(0.974, 1.06)		CYP2C8, CYP2C19, CYP3A, P-gp, or BCRP provided in their approved product labeling
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	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

	day then QD (once daily) for 10 days				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 "Dosage/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 moderate CYP3A inhibitors.
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]	
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

Bosentan [c] (Moderate CYP3A Inducer)	125 mg BID	200 mg QD	0.80 (0.79, 0.81)	0.73 (0.72, 0.75)[d]	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").
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.

Undesirable effects

Summary of the safety profile

The summary of the safety profile and Table 4 lists the adverse drug reactions (ADRs) associated with Jaypirca used as a monotherapy from clinical study data. The ADRs are based on pooled data from 593 patients treated with Jaypirca monotherapy 200 mg QD starting dose with no dose escalation in a phase 1/2 clinical study.

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

The most common adverse reactions of any grade (≥15%), were neutropenia (25.6%), fatigue (28.3%), diarrhea (24.1%), contusion (19.1%), COVID-19 (18.9%), anaemia (17.2%), nausea (16.9%), dyspnoea (16.4%), and cough (16.2%).

Serious adverse reactions occurred in 45% of patients who received Jaypirca. Serious adverse reactions that occurred in ≥2% of patients were pneumonia (6.4%), COVID-19 pneumonia (5.9%), COVID-19 (2.9%), febrile neutropenia (2.7%), sepsis (2.7%), and anaemia (2.2%). Fatal adverse reactions occurred in 7.6% of patients, most commonly due to infections (4.4%) including COVID-19 (0.8% of all patients).

Adverse reactions led to dosage reductions in 5.2%, treatment interruption in 40.8%, and permanent discontinuation of Jaypirca in 9.3%. No adverse reactions resulted in dosage modification in >5% of patients. No adverse reactions resulted in permanent discontinuation of Jaypirca in >1% of patients.

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: ADRs of patients treated with Jaypirca monotherapy[a] at 200 mg QD

System organ class (MedDRA)	ADR	Frequency category (%) (All grades) N=593	Grade ≥3[a] (%)
Blood and lymphatic system disorders	Neutropenia[b]	Very common (27.0)	23.4
	Anaemia[b]	Very common (18.0)	10.5
	Thrombocytopenia[b]	Very common (16.7)	8.9
	Lymphocytosis[b]	Common	3.5
	Lymphocyte count decreased	Very common (30.6)	11.8
Eye disorders	Vision changes[c]	Common	0.5
Cardiac disorders	Atrial fibrillation	Common	1.5
	Atrial Flutter	Uncommon	0.0
Gastrointestinal disorders	Diarrhea	Very common (24.1)	1.2
	Nausea	Very common (16.9)	0.2
	Abdominal pain	Very common (12.6)	1.2
Hepato biliary disorders	AST increased	Very common (21.3)	1.0
	ALT increased	Very common (17.9)	1.4
	Lipase increased	Very common (18.8)	7.4
General disorders and administration site conditions	Fatigue	Very common (28.3)	1.7
	Pyrexia	Very common (14.5)	1.2
	Oedema[c]	Very common (16.5)	0.7
Infections and infestations	Pneumonia	Very common (10.5)	7.1
	Upper respiratory tract infection	Common	0.0
	Urinary tract infection	Common	1.2
	Sepsis[c]	Common	5.9
Injury, poisoning, and procedural complications	Contusion	Very common (19.1)	0.2
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (14.7)	0.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Secondary primary malignancies[c]	Common	2.9
Nervous system disorders	Headache	Very common (11.8)	0.7
	Peripheral Neuropathy[c]	Very Common (14.3)	1.7
	Dizziness	Common	0.0
Renal and urinary disorders	Hematuria	Common	0.0
	Blood creatinine increased	Very common (30.2)	1.0
Respiratory, thoracic, and mediastinal diaorders	Epistaxis	Common	0.0

Skin and subcutaneous tissue disorders	Rash[b]	Very common (18.5)	0.8
	Petechiae	Common	0.0
Vascular disorders	Haematoma	Common	0.2
	Bleeding[C]	Very common (36.4)	3.0
	Calcium decreased	Common	1.2
Investigations	Potassium decreased	Very common (15.2)	1.2
	Sodium decreased	Very common (24.4)	0.7
	Alkaline phosphatase increased	Very common (14.7)	0.5
	Potassium increased	Very common (10.1)	0.2
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 41% of the overall safety popuation in BRUIN who have received 200 mg daily dose. The median time to onset of lymphocytosis was 1.1 weeks, with 75% of cases occurring within 2.0 weeks, and the median duration was 15.0 weeks.

Specific Populations

Elderly

Of the patients with MCL who received the 200 mg dose of Jaypirca in BRUIN, 93 (78%) were 65 years of age and older and 39 (33%) were 75 years and older (see “Clinical efficacy”). In the pooled safety population in patients with hematologic malignancies, 392 (67%) were 65 years of age and older, while 153 (26%) 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 ElViS 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

not yet assigned

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).

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 91300 h*ng/mL (41%) and 6460 ng/mL (26%), 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 32.8 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 2.02 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 27-95 years), sex (394 males and 201 females), and body weight (range 35.7-152.5 kg), race (White 86%, Asian 7%) 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 consisted of decreased size, weight, or cellularity of lymphoid organs; decreases in B lymphocytes and other markers of immune system function; and minimal to mild corneal lesions.

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 patianta 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: 30 tablets(A)
Jaypirca 100 mg: 30, 60 tablets (A)

Marketing authorisation holder

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

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