# Jaypirca ®

# (pirtobrutinib)

50 mg and 100 mg, film-coated tablets

## Summary of Risk Management Plan (RMP)

**Summary of the risk management plan (RMP) for Jaypirca (pirtobrutinib)**

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.
The RMP summary of Jaypirca is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le medicament "approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Jaypirca in Switzerland is the „Arzneimittelinformation/ Information sur le médicament"(see www.swissmedicinfo.ch) approved and authorized by Swissmedic.
Eli Lilly is fully responsible for the accuracy and correctness of the content of this published summary RMP of Jaypica.

## I. The Medicine and What It Is Used For

Pirtobrutinib is proposed as a single agent for the treatment of adult patients with 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 SPC for the full indication). It contains pirtobrutinib as the active substance and it is given by oral dosing in the form of a film-coated tablets in dose strengths of 50 mg or 100 mg.

## II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of pirtobrutinib, together with measures to minimise such risks and the proposed studies for learning more about pirtobrutinib's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information about the safety risks and the ways to minimize are included in the safety section, warnings and precautions, and advice on correct use, in the package leaflet and SPC addressed to patients and healthcare professionals respectively.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of pirtobrutinib is not yet available, it is listed under ‘missing information’ below.

## II.A. List of Important Risks and Missing Information

Important risks of pirtobrutinib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of pirtobrutinib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| **List of Important Risks and Missing Information** | |
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| **Important identified risks** | Serious infections<br>Atrial fibrillation and atrial flutter<br>Serious haemorrhage |
| **Important potential risks** | Second primary malignancies |
| **Missing information** | Exposure and safety in patients with moderate and severe hepatic impairment<br>Long-term Safety (>2 years) |

## II.B. Summary of Important Risks

| **Important identified Risk : Serious infections** | |
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| Evidence for linking the risk to the medicine | The occurrence of serious infections has the potential to impact the risk-benefit balance of pirtobrutinib. Grades ≥3 events observed in 17.7% of patients (2.8% of patients with events deemed related to pirtobrutinib by the investigator) and 29 (4.0%) patients with fatal events due to infection, of which 3 (Enterococcus *faecium*-related septic shock, COVID-19 pneumonia, and pneumonia necrotizing) were considered related to pirtobrutinib by the investigator.<br><br>Serious infections have been commonly reported in patients taking other BTK inhibitors, nevertheless, sustained increases in serum IgA levels induced by ibrutinib and acalabrutinib have been observed, and this finding has been correlated with a lower risk of developing infections with long-term BTK inhibitor therapy.<br><br>Although the frequency of serious infections in Study 18001 is lower when compared to other BTK inhibitors and patients with B-cell malignancies are predisposed to infections, serious infections are a class label risk with a known mechanism of action, described in Section Undesirables effects of the SPC and have potential for severe clinical outcomes; therefore, considered an important identified risk for pirtobrutinib. This risk will be closely monitored and further characterised in the Phase 3 clinical trials. |
| Risk factors and risk groups | Identified risk factors for the occurrence of serious infections include neutropenia (with longer duration and severity of neutropenia increasing the risk; Crawford et al 2004), delayed antimicrobial therapy initiation and patient-related factors (e.g., age, previous comorbidities, nutritional status, performance status, prior chemotherapy. It has been described that ≥ 3 prior treatments, diabetes and liver disease have been associated with the development of opportunistic infections in patients treated with ibrutinib (Rogers et al 2019). |
| Risk minimisation measures | Routine risk communication:<br>- Swiss SPC Sections Warnings and precautions, Dosage/Administration and Undesirable effects<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>- Recommendation to consider prophylaxis in patients who are at increased risk for opportunistic infections is included in Swiss SPC Section Warnings and precautions.<br>- Guidance on dose adjustment based on the grade of infection and whether it occurs with neutropenia is included in Swiss SPC Sections Dosage/Administration and Warnings and precautions. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Not applicable. |

| **Important Identified Risk: atrial fibrillation and atrial flutter** | |
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| Evidence for linking the risk to the medicine. | Atrial fibrillation and atrial flutter are considered class effects based on the safety profile of other BTK inhibitors, although they are less frequently reported with the second-generation (and more selective) covalent agents/ irreversible binding (*i.e.*, acalabrutinib and zanubrutinib). |

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| | Considering atrial fibrillation and atrial flutter are known adverse reaction for both first and second generation BTK inhibitors with suggested mechanisms of actions and described in Section Undesirables effects of the SPC, atrial fibrillation and atrial flutter are considered important identified risks and will be further characterised in the Phase 3 clinical trials. |
| Risk factors and risk groups | Patients at risk for the occurrence of atrial fibrillation and atrial flutter include those with a history of coronary artery disease (especially if complicated with acute myocardial infarction or heart failure; Crenshaw et al 1997), congestive heart failure (Santhanakrishnan et al 2016), hypertension (Krahn et al 1995) and valvular heart disease (Grigioni et al 2002). Other conditions that predispose the occurrence of atrial fibrillation and atrial flutter include infectious events (Musher et al 2007), hyperthyroidism (Woeber 1992), obesity (Nalliah et al 2016) and alcohol consumption (Ettinger et al 1978). |
| Risk minimisation measures | Routine risk communication:<br>- Swiss SPS Sections Dosage/Administration and Warnings and Precautions.<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>- Recommendation to monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated is included in Swiss SPC Section Warnings and precautions.<br>- Guidance on dose adjustment based on the grade of atrial fibrillation/atrial flutter is included in Sections Dosage/Administration and Warnings and precautions. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Not applicable |
| **Important Identified Risk: Serious haemorrhage** | |
| Evidence for linking the risk to the medicine. | Serious haemorrhagic events have been reported at a low frequency in Study 18001, compared with that expected from a highly selective BTK inhibitor. However, clinically significant events have been observed which included higher grade and fatal events. Since haemorrhage is considered a class effect and characterised as an important identified risk for the approved BTK inhibitors, the risk of serious haemorrhage will be classified as an important identified risk. |
| Risk factors and risk groups | Patients presenting with severe thrombocytopenia are at increased risk of serious haemorrhagic events (Neunert et al 2015). Other reported risk factors for the occurrence of major haemorrhage in patients with MCL and other haematologic malignancies include history of major haemorrhage, concomitant use of anticoagulants (for example, warfarin, heparin, enoxaparin) and antiplatelets (for example, acetylsalicylic acid, clopidogrel), renal disease, anaemia, thrombocytopenia, and alcohol abuse (Georgantopoulos et al. 2019, Dmitrieva et al. 2020).<br><br>General medical conditions associated with increased propensity for haemorrhagic events include acquired coagulopathies, inherited bleeding dysfunctions, hepatopathy, renal dysfunction (leading to uraemia- |

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| | induced platelet dysfunction; Boccardo et al. 2004), and connective tissue disorders leading to haematologic abnormalities. |
| Risk minimisation measures | Routine risk communication:<br>- Swiss SPC Sections Dosage/Administration, Warnings and precautions, and Undesirable effects.<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>- Recommendation to monitor patients for signs and symptoms of bleeding is included in Swiss SPC Section Warnings and precautions.<br>- Recommendation to consider the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery depending on the type of surgery and risk of bleeding is included in Swiss SPC Section Warnings and precautions.<br>- Guidance on dose adjustment based on the grade of the bleeding event and whether it occurs with thrombocytopenia is provided in Swiss SPC Sections Dosage/Administration and Warnings and precautions. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: Not applicable |

**Important potential risks:** Second primary malignancies (SPM)

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| Evidence for linking the risk to the medicine: | Second primary malignancy has been described in association with other BTK inhibitors and is included as an important potential risk ("other malignancies [excluding non-melanoma skin cancer]") and identified risk ("non-melanoma skin cancer") for ibrutinib and as an important identified risk ("second primary malignancy") for acalabrutinib.<br>There have been cases of SPM observed in Study 18001 (6.6% of patients) and most of those were non-melanoma skin cancers (4.6%). Given there is a high predisposition of skin cancers among patients with the types of hematologic malignancies evaluated in Study 18001 and considering that such events are not uncommon in the elderly population, SPM is considered to be an important potential risk for pirtobrutinib since the association with the drug is still unclear. |
| Risk factors and risk groups: | Smoking, advanced age, male gender, specific comorbidities (for example, chronic obstructive pulmonary disease, cirrhosis), previous treatment (radiotherapy, fludarabine-combination chemotherapy, BTK inhibitors), significant and unprotected sun exposure are considered risk factors for the occurrence of second primary malignancy in patients with MCL or CLL. |
| Routine risk communication: | The SPC Section Warnings and precautions<br>Routine risk minimization activities recommending specific clinical measures to<br>address the risk:<br>- Recommendation to monitor patients for the appearance of skin cancers and<br>advise protection from sun exposure is included in the SPC Section Warnings and precautions. |

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| **Missing information:** Exposure and safety in patients with moderate and severe hepatic impairment | |
| | Data from the clinical pharmacology Study LOXO-BTK-20012, in participants with mild, moderate, and severe hepatic impairment, systemic exposure of pirtobrutinib was similar between subjects with mild hepatic impairment and normal hepatic function and was approximately 15% and 21% lower in subjects with moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. Hepatic function has no effect on the $C_{max}$ of pirtobrutinib. No adjustment of the dose of pirtobrutinib is required for patients with mild to severe hepatic impairment.<br>The Swiss SPC is updated based on the safety and pharmacokinetic data from this study. |
| **Missing information:** Long-term Safety (>2 years). | |
| | No specific measures except for recommendation to monitor patients for the<br>appearance of skin cancers and advise protection from sun exposure is included in the SPC Section Warnings and precautions. |

SPC = Summary of Product Characteristics.

## II.C. Post-authorisation Development Plan

### II.C.1. Studies that Are Conditions of the Marketing Authorisation

The following study is a condition of the marketing authorisation:

Study short name: **LOXO-BTK-20019 (BRUIN MCL-321; Study 20019)**

Purpose of the study: The study will compare pirtobrutinib, a non-covalent BTK inhibitor versus investigator's choice of covalent BTK inhibitor therapy, evaluating the differences in efficacy, safety and tolerability in this patient population and confirming the activity and safety of pirtobrutinib in patients with relapsed MCL.

The primary objective is to compare PFS (progression free survival) of pirtobrutinib as monotherapy to investigator choice of covalent BTK inhibitor monotherapy in patients with previously treated MCL.

### II.C.2. Other Studies in Post-authorisation Development Plan

None