CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216059Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216059
PDUFA Goal Date	January 27, 2023
OSE RCM #	2021-2378; 2021-2380
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D.
Review Completion Date	January 10, 2023
Subject	Evaluation of the need for a REMS
Established Name	Pirtobrutinib
Trade Name	Jaypirca
Name of Applicant	Loxo Oncology Inc.
Therapeutic Class	Kinase inhibitor
Formulation(s)	50 mg and 100 mg tablets
Dosing Regimen	200 mg once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Jaypirca (pirtobrutinib) is necessary to ensure the benefits outweigh its risks. Loxo Oncology Inc. submitted a New Drug Application (NDA) 216059 for pirtobrutinib with the proposed indication for the treatment of adult patients with Mantle cell lymphoma (MCL) who have been previously treated with a bruton's tyrosine kinase (BTK) inhibitor. The serious risks associated with the use of pirtobrutinib are infections, hemorrhage, cytopenias, atrial fibrillation and atrial flutter, second primary malignancies, and embryo-fetal toxicity. The applicant did not submit a REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Hematology Malignancies 2 (DHM2) have determined that a REMS is not necessary to ensure the benefits of pirtobrutinib outweigh its risks. Based on the efficacy and safety information currently available, the clinical reviewer stated that pirtobrutinib shows clinically meaningful benefit and recommends approval of pirtobrutinib as a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor. The review team concluded that the overall tolerability of pirtobrutinib in patients with B-cell hematologic malignancies, such as MCL (b) (4) was favorable and characterized by toxicities that are common to the drug class and/or the underlying disease setting. The safety profile is similar to other BTK inhibitors approved for similar indications which do not require a REMS. If approved, labeling will be similar to the currently approved other BTK inhibitors, such as zanubrutinib (Brukinsa). Management of the adverse events of pirtobrutinib will be communicated in Warnings and Precautions, Patient Counseling Information, and the Patient Package Insert (PPI).

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for Jaypirca (pirtobrutinib) is necessary to ensure the benefits outweigh its risks. Loxo Oncology Inc. submitted a New Drug Application (NDA) 216059 for pirtobrutinib with the proposed indication (b) (4) .[1] This application is under review in the Division of Hematology Malignancies 2 (DHM2). The applicant did not submit a REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Pirtobrutinib is a new molecular entity (NME) NDA type 505(b)(1) pathway application.[a] This product is a noncovalent inhibitor of BTK. BTK is a signaling protein of the B-cell antigen receptor (BCR) 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 both wild type BTK and BTK harboring C481 mutations, leading to inhibition of BTK kinase activity.[1] Pirtobrutinib is proposed to be supplied as 50 mg and 100 mg tablets. The recommended dosage of pirtobrutinib is 200 mg

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

administered once daily taken until disease progression or unacceptable toxicity. [b,1] Pirtobrutinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for pirtobrutinib (NDA 216059) relevant to this review:

- 08/29/2018 Investigation New Drug (IND) 139876 submission for pirtobrutinib received.
- 05/27/2022: NDA 216059 submission for pirtobrutinib with the proposed indication for the treatment of adult patients with MCL who have been previously treated with a BTK inhibitor, received.
- 10/20/2022: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Post Mid-cycle meeting that based on the currently available data, there were no safety issues that require a REMS for pirtobrutinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

MCL is a distinctive subtype of B-cell non-Hodgkin lymphoma (NHL) which represents 3% to 10% of all non-Hodgkin Lymphoma.[2] MCL is more common in men (3 to 1), and the median age at diagnosis ranges 60 to 70 years old.[3] In 2016 the World Health Organization classified MCL into two distinct categories; classic MCL, which represents 80–90% of cases, which is characterized by lymphadenopathy and typically exhibits aggressive behavior, and the more indolent leukemic non-nodal MCL.[4] The annual incidence of MCL is one case per 200,000 people.[3,c] MCL is considered as an incurable aggressive B cell lymphoma with a median survival of 3-5 years.[2,d] NHL represents approximately 4% of all cancer diagnoses and is the seventh most common cancer. The expected number of new cases of NHL in the United States in 2022 is 80,470, with 20,250 expected deaths due to the disease.[5,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Chemoimmunotherapy regimens comprise the standard first-line treatment options for patients with MCL. Although a subset of patients with indolent disease may undergo observation, most patients ultimately require therapy.[6] MCL has a wide spectrum of clinical behavior, where some patients present with asymptomatic monoclonal MCL-type lymphocytosis or non-bulky lymphadenopathy, while others exhibit a highly aggressive disease with rapidly progressive lymphadenopathy, cytopenias, or extra-nodal

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

involvement including of the central nervous system. While the former group of patients may be subjected to a watch and wait approach for months to years, the latter majority require systemic therapy soon after the initial diagnosis.[4] Several regimens prolong response durations, but none is curative. The current treatment approach is based on patient age and fitness, with fit patients receiving intensive combination therapies incorporating rituximab and cytarabine, with or without consolidation autologous stem cell transplantation (ASCT), whereas older or unfit patients or those who are transplant ineligible are treated with combination chemo-immunotherapy. Regimens such as bendamustine/ rituximab are recognized as standard approaches in addition to R-CHOP (rituximab/cyclophosphamide/ doxorubicin/vincristine/prednisone) and VR-CAP (bortezomib/rituximab/cyclophosphamide/ doxorubicin/prednisone).[6,7]

Evolving strategies seek to examine chemotherapy-free treatment paradigms and/or to incorporate newer therapies like targeted agents, including the BTK inhibitors. There are currently three BTK inhibitors approved in the US: ibrutinib[8] (approved 2013, NDA 205552), acalabrutinib[9] (approved 2017, NDA 210259), and zanubrutinib[10] (approved 2019, NDA 213217). None of these products have a boxed warning in their labels, nor was a REMS required for approval. The BTK inhibitors showed unprecedented clinical activity in patients with relapsed/refractory disease and are now second-line options for patients following chemoimmunotherapy.[6,7]

New emerging strategies use prognostic markers, such as minimal residual disease (MRD), to guide therapy decisions.[7] The development of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (CAR-T therapy) represents a major advance in the treatment of patients with chemorefractory B-cell malignancies. U.S. FDA approved Tecartus (brexucabtagene autoleucel)[11] in July 2020 for all patients with relapsed/refractory MCL. Brexucabtagene autoleucel was approved with a REMS that included elements to assure safe use (ETASU) with a goal to mitigate the risk of cytokine release syndrome (CRS) and neurological toxicities by ensuring that that hospitals and their associated clinics that dispense brexucabtagene autoleucel are specially certified and have on-site, immediate access to tocilizumab and also ensuring that those who prescribe, dispense, or administer brexucabtagene autoleucel are aware of how to manage the risks of CRS and neurological toxicities. Real-world experience with brexucabtagene autoleucel was recently reported; in a retrospective study of patients treated with brexucabtagene autoleucel across 14 U.S. centers (107 leukapheresed, 93 reinfused), 64 the ORR in 81 patients with efficacy-evaluable disease was 86%, with a CR rate of 64%. Grade 3 or higher cytokine release syndrome and neurotoxicity occurred in 8% and 33% of patients, respectively.[6] Therefore, while CAR-T therapy has been recently approved, this treatment modality carries significant logistical challenges as well as the potential severe toxicities of the therapy, which limits CAR-T to those who are fit and have slowly progressing disease in order to be able to make it through treatment.[12,13,14] It is important to also consider that patients can relapse following CAR-T with no subsequent approved therapy available.[12] Despite the availability of highly effective frontline therapies for MCL, an unmet need for treatment options persists for patients experiencing disease relapse.

4 Benefit Assessment

The efficacy of pirtobrutinib was evaluated in patients with MCL in study BRUIN [NCT03740529], an open-label, international, single-arm study of pirtobrutinib monotherapy. The efficacy was based on 120 patients with MCL treated with pirtobrutinib who were previously treated with a BTK inhibitor. Pirtobrutinib 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) and 80% of patients were male. 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 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%). 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. Additionally, the Kaplan-Meier estimate for the DOR rate at 6 months was 65.3% (95% CI: 49.8, 77.1). Efficacy results are shown in Table 1.[1,12,e]

Table 1: Efficacy Results per IRC in Patients with MCL Previously Treated with a BTK Inhibitor [1,12,e]

Outcome	**Pirtobrutinib 200 mg once daily (N=120)**
Overall Response Rate [a, b]	
ORR, n	60 (50%)
(95% CI, %)	41, 59
CR, n	15 (13%)
PR, n	45 (38%)
Time to Response	
Median (range), months	1.8 (0.8, 4.2)
Duration of Response [c]	
Number censored, n	36
Median DOR months (95% CI)	8.3 (5.7, NE)

CI, confidence interval; CR, complete response; DOR, duration of response; PR, partial response; NE, not estimable.
[a] PET-CT scans were utilized in response assessments (in 41% of patients), with the remainder being assessed by CT scans only.
[b] ORR using CT scan-based assessments in all patients was 48% (95% CI: 38, 57) and CR rate was 13%.
[c] Based on Kaplan-Meier estimation. Estimated median follow-up was 7.3 months.

The clinical reviewer stated that the IRC-assessed ORR was 50% (95% CI: 41, 59) and CR rate was 13%, with median time to response of 1.8 months. Median DOR per IRC was 8.3 months (95% CI: 5.68, NE). Of the 60 patients who achieved an objective response, 35% maintained responses for at least 6 months and 15% maintained responses for at least 12 months. Due to the notable degree of censoring within 6-9 months of onset of response, the assessment of durability of response with pirtobrutinib is limited. Additionally, there are notable rates of disease progression in responders within the first 6-9 months of treatment and there are limited numbers of patients who maintained responses beyond 6 months. The

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

clinical reviewer also stated that the efficacy population represents a refractory patient population with prior BTK inhibitor treatment, so the response rate, which is coupled with demonstration of durability in about 1/3 of patients, is supportive of clinically meaningful efficacy in patients with R/R MCL with at least 2 prior lines of therapy including a BTK inhibitor.[12,e]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for pirtobrutinib. The safety of pirtobrutinib was evaluated in the BRUIN trial in patients with MCL who received a prior BTK inhibitor (see Section 4: Benefit Assessment). The trial required a platelet count ≥ 50 x 10^9/L, absolute neutrophil count ≥ 75 x 10^9/L, hepatic transaminases < 2.5 times upper limit of normal (ULN), and an ECOG performance status of 0 to 2. The trial excluded patients with active central nervous system (CNS) involvement by lymphoma, significant cardiovascular disease, major bleeding, or grade ≥ 3 arrhythmia with a prior BTK inhibitor, prolonged QTc interval, or need for a strong CYP3A inhibitor or inducer or strong P-gp inhibitor.[1]

The pooled safety population (n=583) reflects the exposure to pirtobrutinib as a single-agent, administered at 200mg once daily in 583 patients with hematologic malignancies in the BRUIN study, which reflects the data for Warnings and Precautions. Among these 583 patients, the median duration of exposure was 7.5 months, 56% were exposed for at least 6 months and 29% were exposed for at least one year. In this pooled safety population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were decreased neutrophil count (41%), decreased hemoglobin (37%), decreased platelet count (27%), fatigue (27%), musculoskeletal pain (26%), decreased lymphocyte count (24%), bruising (20%), and diarrhea (20%).[1]

Deaths

There was a total of 35 (27.3%) deaths across MCL safety population (n=128). Overall, the most common cause of death was progressive disease (20 [15.6%] patients), adverse event (9 [7%] patients) and other (6 [4.7%] patients). Fatal AEs occurred in 6% of patients treated with pirtobrutinib, most commonly infections (6 [4.7%]), and included cases of pneumonia, mucormycosis infection, and streptococcal infection, and one of each event (0.8%) was reported as respiratory failure, bleeding disorder and a sudden death with unknown cause.[12] Fatal adverse reactions within 28 days of the last dose of pirtobrutinib occurred in 7% of patients, most commonly due to infections (4.7%) including COVID-19 (3.1% with 75of all patients).[1]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 38% of patients who received pirtobrutinib. Serious adverse reactions that occurred in ≥2% of patients were pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). Adverse reactions led to dosage reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of pirtobrutinib in 9%. Adverse reactions that resulted in dosage modification in > 5% of patients included pneumonia and neutropenia. Adverse reactions which resulted in permanent discontinuation of pirtobrutinib in > 1% of patients included pneumonia.[1]

Similar to other BTK inhibitors, such as zanubrutinib (Brukinsa)[10], if approved, labeling will include the risks of are infections, hemorrhage, cytopenias, atrial fibrillation and atrial flutter, second primary malignancies, and embryo-fetal toxicity in the Warnings and Precautions section.

5.1 INFECTIONS

In the clinical trial, fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients treated with pirtobrutinib. In the pooled population, 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 pirtobrutinib have included, but are not limited to, *Pneumocystis jirovecii* pneumonia and fungal infection. Similar to zanubrutinib (Brukinsa)[10], labeling instructs healthcare providers to consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients who are at increased risk for infections, including opportunistic infections. The labeling also instructs to monitor patients for signs and symptoms of infection, evaluate promptly, treat appropriately, and based on severity, reduce dose, temporarily withhold, or permanently discontinue pirtobrutinib. Monitoring and dosage modifications for toxicities to address the safety issues with pirtobrutinib will also be included in the Dosage and Administration section of the label.[1]

5.2 HEMORRHAGE

In the clinical trial, fatal and serious hemorrhage has occurred with pirtobrutinib. In the pooled population in the clinical trial, major hemorrhage of grade 3 or higher bleeding or any central nervous system bleeding occurred in 2.4% of 583 patients treated with pirtobrutinib, 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 pirtobrutinib without antithrombotic agents and 0.7% of patients with antithrombotic agents. The labeling instructs to consider the risks and benefits of antithrombotic agents when co-administered with pirtobrutinib. Similar to zanubrutinib (Brukinsa)[10], labeling instructs to monitor patients for signs of bleeding, and based on severity of bleeding, reduce dose, temporarily withhold, or permanently discontinue pirtobrutinib. The labeling also recommends considering the benefit-risk of withholding pirtobrutinib for 3 to 7 days pre– and post-surgery depending upon the type of surgery and risk of bleeding. Monitoring and dosage modifications for toxicities to address the safety issues with pirtobrutinib will also be included in the Dosage and Administration section of the label.[1]

5.3 CYTOPENIAS

In the clinical trial, grade 3 or 4 cytopenias, including neutropenia (24%), anemia (11%), and thrombocytopenia (11%) have developed in patients treated with pirtobrutinib. Grade 4 neutropenia developed in 13% of patients and Grade 4 thrombocytopenia developed in 5% of patients. Similar to zanubrutinib (Brukinsa)[10], labeling instructs to monitor complete blood counts regularly during treatment, and based on severity, reduce dose, temporarily withhold, or permanently discontinue pirtobrutinib. Monitoring and dosage modifications for toxicities to address the safety issues with pirtobrutinib will also be included in the Dosage and Administration section of the label.[1]

5.4 ATRIAL FIBRILLATION AND ATRIAL FLUTTER

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. Similar to zanubrutinib (Brukinsa)[10], labeling states that patients with cardiac risk factors, such as hypertension, or previous arrhythmias may be at increased risk. The labeling instructs to monitor for signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea) and manage appropriately, and based on severity, reduce dose, temporarily withhold, or permanently discontinue pirtobrutinib. Monitoring and dosage modifications for toxicities to address the safety issues with pirtobrutinib will also be included in the Dosage and Administration section of the label.[1]

5.5 SECOND PRIMARY MALIGNANCIES

In clinical trial, 6% of 583 patients treated with pirtobrutinib monotherapy were reported second primary malignancies, including non-skin carcinomas. 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. Similar to zanubrutinib (Brukinsa)[10], labeling instructs to advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.6 EMBRYO-FETAL TOXICITY

Similar to other BTK inhibitors, based on its mechanism of action and findings from animal data, pirtobrutinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of pirtobrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including embryo-fetal mortality and malformations at maternal exposures (AUC) approximately 3-times the recommended dose of 200 mg once daily. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception during treatment with pirtobrutinib and for one week after the last dose will be communicated in the Use in Specific Populations section of the label.[1]

6 Expected Postmarket Use

Similar to other BTK inhibitors, if approved, pirtobrutinib will be used in both inpatient and outpatient settings. It is expected that oncologists, familiar with the management of toxicities such as infections, hemorrhage, cytopenias, atrial fibrillation and atrial flutter, second primary malignancies, and embryo-fetal toxicity, will be the likely prescribers of pirtobrutinib.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for pirtobrutinib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for pirtobrutinib, this reviewer considered the patient population, seriousness of the disease, expected

benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Pirtobrutinib is a BTK inhibitor, with the proposed indication for the treatment of adult patients with MCL who have been previously treated with a BTK inhibitor. MCL is considered as an incurable aggressive B cell lymphoma with a median survival of only 3-5 years. NHL represents approximately 4% of all cancer diagnoses and is the seventh most common cancer. Despite the availability of highly effective frontline therapies for MCL, an unmet need for treatment options persists for patients experiencing disease relapse. Based on the efficacy and safety information currently available, the clinical reviewer stated that pirtobrutinib shows clinically meaningful benefit and recommends approval of pirtobrutinib for the treatment of adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor.[12]

DRM and DHM2 have determined that if approved, a REMS is not necessary to ensure the benefits of pirtobrutinib outweigh its risks. Pirtobrutinib appeared efficacious in its primary outcome of ORR and secondary outcome of DOR, and its risks can be communicated and managed through labeling.[1,12] The clinical reviewer stated that the efficacy population represents a refractory patient population with prior BTK inhibitor treatment, therefore the response rate, which is coupled with demonstration of durability in about 1/3 of patients, is supportive of clinically meaningful efficacy in patients with R/R MCL with at least 2 prior lines of therapy including a BTK inhibitor.[12] The most concerning adverse reactions observed with the use of pirtobrutinib are risks for infections, hemorrhage, cytopenias, atrial fibrillation and atrial flutter, second primary malignancies, and embryo-fetal toxicity, which are the same as in the currently approved BTK inhibitors, such as zanubrutinib (Brukinsa).[10] Monitoring and dosage modifications for toxicities to address the safety issues with pirtobrutinib will also be included in both the Warnings and Precautions and the Dosage and Administration sections of the label. It is expected that oncologists, familiar with the management of these toxicities, will be the likely prescribers of pirtobrutinib. The review team concluded that the overall tolerability of pirtobrutinib in patients with B-cell hematologic malignancies, such as MCL and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), was favorable and characterized by toxicities that are common to the drug class and/or the underlying disease setting.[12] None of the previoulsy approved BTK inhibtiors have a boxed warning in their labels, nor was a REMS required for approval. At the time of this review, none of these risks will receive a boxed warning in the label[1], however labeling negotiations were still ongoing with the Applicant. If pirtobrutinib is approved, similar to zanubrutinib (Brukinsa), Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with pirtobrutinib, as well as information to be included in Patient Counseling Information, and in the PPI. To better characterize safety the Agency is planning to issue three post-marketing required (PMR)s, which include a confirmatory trial in mantle cell lymphoma, a safety PMR to evaluate longer-term safety, and a safety PMR to further evaluate second primary malignancies.[15]

9 Conclusion & Recommendations

DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of pirtobrutinib for the treatment of adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor. The management of the risks associated with pirtobrutinib treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

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[10] Brukinsa. Prescribing Information (last updated 9/2021).

[11] Tacartus. Prescribing Information (last updated 9/2022).

[12] Division of Hematology Malignancies 2 (DHM2) Assessment Aid (draft) for pirtobrutinib, NDA 216059, dated December 23, 2022.

[13] CAR T-cell Therapy and Its Side Effects. American Cancer Society. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html. Accessed December 7, 2022.

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