CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761258Orig1s000

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	BLA
Application Number	761258
PDUFA Goal Date	October 16, 2022
OSE RCM #	2021-1084; 2021-1086
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS	Laura Zendel, Pharm.D.
Design and Evaluation	
Review Completion Date	October 03, 2022
Subject	Evaluation of the need for a REMS
Established Name	penpulimab-kcqx
Trade Name	Pending Review
Name of Applicant	Akeso Biopharma Co., Ltd.
Therapeutic Class	Programmed death receptor-1 (PD-1) blocking antibody
Formulation(s)	100 mg/10 mL (10 mg/mL) solution in a single-dose vial
Dosing Regimen	200 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity up to 24 months

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for penpulimab-kcqx is necessary to ensure the benefits outweigh its risks. Akeso Biopharma Co., Ltd. submitted a Biologic Licensing Application (BLA) 761258 for penpulimab-kcqx with the proposed indication for the treatment of adult [redacted] (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma (NPC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. The serious risks associated with the use of penpulimab-kcqx are severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT) and embryo-fetal toxicity. The Applicant did not submit a REMS or risk management plan with this application; but proposed describing these risks in the Prescribing Information (PI) that includes Warnings and Precautions, a Medication Guide, as well as information to be included in Patient Counseling Information.

The Division of Risk Management (DRM) and the Division of Oncology Disease 2 (DO2) have determined that a REMS is not necessary to ensure the benefits of penpulimab-kcqx outweigh its risks. NPC is an epithelial carcinoma arising from the nasopharyngeal mucosal lining. It has a high propensity to metastasize to distant sites and poses a significant risk for isolated local recurrences after radiation for locally advanced disease. Currently, there are no FDA-approved therapies for the treatment of patients with metastatic NPC in the United States (US). Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease. Penpulimab-kcqx appeared efficacious in its primary outcome of objective response rate (ORR) and secondary outcomes of duration of response (DOR), and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer stated that penpulimab-kcqx shows clinically meaningful benefit and recommends approval of penpulimab-kcqx using the accelerated approval pathway for the treatment of adult [redacted] (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. If approved, labeling will be similar to the currently approved other PD-1 blocking antibodies such as dostarlimab-gxly (Jemperli). Management of the adverse events of penpulimab-kcqx will be communicated in Warnings and Precautions, Patient Counseling Information, and the Medication Guide. The review team concluded the observed safety profile is acceptable when assessed in the context of a life-threatening disease with unmet medical need.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for penpulimab-kcqx is necessary to ensure the benefits outweigh its risks. Akeso Biopharma Co., Ltd. submitted a Biologic Licensing Application (BLA) 761258 for penpulimab-kcqx with the proposed indication for the treatment of adult [redacted] (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1] This application is under review in the Division of Oncology Disease 2 (DO2). The Applicant did not submit a REMS or risk management plan with this application; but proposed describing these risks in the Prescribing Information (PI) that includes Warnings and Precautions, a Medication Guide, as well as information to be included in Patient Counseling Information.

2 Background

2.1 PRODUCT INFORMATION

Penpulimab-kcqx is a new molecular entity (NME) BLA type 351(a) pathway application.[a] This product is a programmed death receptor-1 (PD-1) blocking antibody. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Penpulimab-kcqx injection is a humanized IgG1 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.[1] Penpulimab-kcqx is proposed to be supplied as 100 mg/10 mL (10 mg/mL) solution in a single-dose vial. The recommended dosage of penpulimab-kcqx is 200 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity, for a maximum of 24 months.[b,1] Penpulimab-kcqx is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for penpulimab-kcqx (BLA 761258) relevant to this review:

- 02/23/2018 Investigation New Drug (IND) 138576 submission for penpulimab-kcqx AK105 received.
- 10/13/2020: Fast Track Designation granted
- 02/23/2021: Orphan Drug Designation granted
- 03/24/2021: Breakthrough Therapy Designation granted
- 07/16/2021: BLA 761258 submission for penpulimab-kcqx with the proposed indication for the treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy, received.
- 12/13/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no safety issues have been identified for penpulimab-kcqx that would require a REMS.
- 06/14/2022: On May 31, 2022, FDA received a submission from the Applicant containing a portion of the outstanding microbial safety data, which triggered a major amendment. The user fee goal date is extended to October 16, 2022.

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

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

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma arising from the nasopharyngeal mucosal lining.[2] Patients remain asymptomatic for long periods and often present with locally advanced or metastatic disease. At presentation, signs and symptoms may include nasal obstruction, epistaxis, serous otitis media, cervical lymphadenopathy, headache, diplopia, and facial numbness.[3] According to the World Health Organization, there are three pathological subtypes of nasopharyngeal carcinoma: keratinizing squamous, non-keratinizing, and basaloid squamous. Non-keratinizing nasopharyngeal carcinoma can be divided into differentiated and undifferentiated tumors. The keratinizing subtype accounts for less than 20% of cases worldwide, and is relatively rare in endemic areas such as southern China. The non-keratinizing subtype constitutes most cases in endemic areas (>95%) and is predominantly associated with Epstein-Barr virus (EBV) infection.[2] According to the International Agency for Research on Cancer, 133,354 new cases of NPC were reported in 2020[c], and approximately 80,008 people died from NPC in 2020 globally.[4,d] NPC is more common in certain parts of North Africa, the Middle East, and Asia, particularly in some areas of China.[5] It is most prevalent in Southern China, where the annual incidence is about 30 cases per 100,000 persons. In contrast, fewer than 1 case per 100,000 persons are reported in the US and Europe.[6] The 5-year survival rate for all people with NPC in the US is 61%.[5] NPC incidence among males is double or triple that among females in most populations.[7] Nasopharyngeal carcinoma has a high propensity to metastasize to distant sites, and poses a significant risk for isolated local recurrences after radiation for locally advanced disease. Due to treatment failure, it caused 65,000 deaths globally in 2010.[8]

3.2 Description of Current Treatment Options

At present, radiotherapy (RT) is the only curative treatment for NPC. Intensity-modulated radiotherapy (IMRT) has become one of the most important achievements in the treatment of NPC.[9] Patients with Stage I disease typically undergo radiation therapy while patients with more advanced disease receive chemoradiotherapy. Although IMRT delivers therapeutic doses to tumors near critical structures in the skull, the irradiation of adjacent tissues is unavoidable because of the inherent restriction arising from the physical properties of the photon beam. On the other hand, proton beam therapy has shown better conformality because the properties of the Bragg peak[e] allow maximum doses to be deposited on the target cancer. The toxicity of proton beam therapy is also less than that of IMRT because proton beam therapy can eliminate the exit dose beyond the target area. IMRT has been recommended as the standard treatment for stage II–IV NPC patients. However, IMRT alone cannot significantly reduce the distant metastasis rate, which is still the major cause of patient death. Concurrent chemoradiation therapy (CCRT) is suitable when treating locoregionally advanced NPC patients.[9]

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[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.*

[e] Plots the energy loss of ionizing radiation during its travel through matter.

Platinum-containing doublet chemotherapy regimens are generally considered the standard first-line systemic therapy for recurrent or metastatic (R/M) NPC. Even though, currently, cisplatin in combination with continuous intravenous infusion of fluorouracil is the global standard treatment used in patients with R/M NPC, gemcitabine (GEM) plus cisplatin (CDDP) has become a standard therapy based on a phase 3 study in several countries, yet this regimen sometimes affects quality of life due to nausea or appetite loss.[10] In a randomized trial of 362 patients, median progression-free survival (PFS) with cisplatin and gemcitabine was 7.0 months compared to 5.6 months with cisplatin and 5-fluorouracil (hazard ratio (HR) 0.55; $p < 0.0001$).[11,12]

At present, the National Comprehensive Cancer Network (NCCN) Guidelines recommend both concurrent chemoradiotherapy with adjuvant chemotherapy or induction chemotherapy followed by concurrent chemoradiation as level 2A evidence, and concurrent chemoradiotherapy alone as level 2B evidence for stage II–IVA nasopharyngeal carcinoma.[12] For patients who have failed first-line platinum-containing chemotherapy and whose disease has relapsed within one year after the chemotherapy regimen, the second-line chemotherapy, including gemcitabine, capecitabine, or paclitaxel, may be considered. However, to date, there is no recognized standard third-line systemic therapy. Increasing evidence suggests that further use of chemotherapy after second- or third-line chemotherapy may not prolong the significant meaningful survival in most patients. It has been reported that NPC is closely associated with EB virus infection, and there is high PD-L1 expression in the tumor, suggesting that PD-1 blockade may be an ideal treatment option for NPC. There are no approved drugs for the treatment of patients with metastatic NPC in US.[13] Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease.

4 Benefit Assessment

The efficacy of penpulimab-kcqx was evaluated in study AK105-202 (NCT03866967), a multicenter, open-label, single-arm trial conducted in China. A total of 111 patients with metastatic non-keratinizing NPC with measurable disease at baseline and who had progressed on or after platinum-based chemotherapy and at least one other line of therapy had initiated penpulimab-kcqx therapy at least 8 months prior to the data cut-off date. The trial excluded patients with a history of autoimmune disease or a medical condition that required immunosuppression. Patients received penpulimab-kcqx 200 mg intravenously every 2 weeks for a maximum of 24 months, or until disease progression or unacceptable toxicity.[1] The median age of patients enrolled in Study AK105-202 was 50 years (range: 21 to 66 years), 76% were male, 100% were Asian, Eastern Cooperative Oncology Group (ECOG) performance score (PS) was 0 (31%) or 1 (69%). Thirty-two percent of patients had non-keratinizing, differentiated NPC, 64% had non-keratinizing undifferentiated NPC, and 4% had non-keratinizing NPC with unknown differentiation. Ten percent of patients had PD-L1 Tumor Proportion Score (TPS) <1%, 50% of patients had PD-L1 TPS 1-49%, and 39% of patients had PD-L1 TPS ≥ 50%. All patients had received prior platinum-based chemotherapy. Sixty-two percent of patients had received 2 prior lines of chemotherapy, and 38% of patients had received 3 or more prior lines of chemotherapy. Ninety-three percent of patients had received prior radiotherapy.[1]

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for penpulimab-kcqx. The primary efficacy endpoint was objective response rate (ORR) by Independent Radiologic Review Committee (IRRC) per RECIST v1.1. The key secondary endpoint was duration of response (DOR). Amongst the 111 patients in

the primary efficacy population, the ORR was 30% (95% CI 21, 39) (data cut off February 3, 2021). Median duration of response (DOR) was not reached (range 3.8, 17.1+), however 39% of the 33 responding patients had a DOR ≥ 9 months.[1,13,f] The efficacy results are summarized in Table 1.[13,13,f] The clinical reviewer stated that the durable ORR observed amongst patients treated with penpulimab-kcqx in AK105-202 provides patients with a meaningful option in a treatment space where there is no FDA-approved therapy. An ORR of large magnitude and long duration is an endpoint reasonably likely to predict clinical benefit in metastatic NPC. Since the primary trial supporting the marketing application was conducted in China only, the patient population is not reflective of the racial and ethnic diversity of U.S. patients with NPC. The clinical reviewer stated that a flexible regulatory approach is warranted in this setting given the higher incidence of NPC in China and lack of FDA-approved therapies for this disease, and the submitted evidence meets the statutory evidentiary standard for accelerated approval with a clinically meaningful response rate and durable responses.[13]

Table 1: Efficacy Results in Study AK105-202 [1,13,f]

Efficacy Parameter	**Penpulimab-kcqx (N=111)**
Objective Response Rate, % (95% CI)	30 (21, 39)
Complete response rate, %	0.9
Partial response rate, %	29
Duration of Response (DOR)	N=33
Median[a], months (range)	NR (3.8+, 22.3+)
Patients with duration of response ≥ 6 months (%)	85

+ Indicates a censored value.
[a] Estimate using Kaplan-Meier method
NR = not reached

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 penpulimab-kcqx. The safety of penpulimab-kcqx for use in NPC was evaluated in Study AK105-202 (see Section 4: Benefit Assessment). Eligible patients had metastatic non-keratinizing NPC and had received prior platinum-based chemotherapy and at least one other line of therapy or had disease progression within 6 months of completion of platinum-based chemotherapy administered as neoadjuvant, adjuvant, or definitive chemoradiation treatment. Among patients who received penpulimab-kcqx, 43% received penpulimab-kcqx for 6 months or more and 19% were exposed for greater than one year.[1]

[f] 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*

The pooled safety population reflects the exposure to penpulimab-kcqx in 372 patients from 4 clinical studies (AK105-101, AK105-201, AK105-202, and AK105-204). Each of these studies was multicenter and open label with AK105-201, AK105-202, and AK105-204 being single arm studies and AK105-101 being a dose escalation and dose expansion study in various patient populations including advanced solid tumors and relapsed or refractory classical Hodgkin lymphoma as well as NPC. In these studies, penpulimab-kcqx was administered at a dosage of 200 mg every 2 weeks. Among the 372 patients, 49% were exposed for 6 months or more and 27% were exposed for 12 months or more. In this pooled safety population, the most common (> 10%) adverse reactions were hypothyroidism, musculoskeletal pain, pyrexia, rash and upper respiratory tract infections and the most common (> 20%) laboratory abnormalities were anemia, increased gamma glutanyl transferase, hypophosphatemia, hyponatremia, hypertriglyceridemia. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were increased gamma glutanyl transferase, hypophosphatemia, hyponatremia, hypertriglyceridemia, anemia and lymphocytopenia.

Deaths

A total of 47 (36.2%) deaths occurred in NPC safety population. A total of 2 (1.5%) deaths occurred within 30 days after the last dose. Eighteen (13.8%) patients had adverse events (AEs) that resulted in death, regardless of causality. Excluding disease progression, AEs with an outcome of death were reported in 7 (5.4%) patients: unexplained death in 3 patients, respiratory failure in 2 patients, septic shock in 1 patient, and sudden death in 1 patient. Drug-related AE leading to death occurred in 2 patients, “death” as PT in both cases, and causality were unable to be assessed in these 2 cases. Most death cases in the clinical studies were related to disease progression. This is consistent with patients’ underlying medical conditions, and possibly concomitant medications. Of the 7 patients with a fatal event (excluding events of disease progression), the clinical reviewer considers only the events of septic shock and three events of “death” to be fatal adverse reactions. The patient who suffered sudden death died after a car accident which more likely contributed to his death. One of the patients who died of respiratory failure likely died of disease progression. The second patient who died of respiratory failure died 46 days after the first dose of penpulimab-kcqx after refusing to follow up and was deemed by the investigator to have died of disease progression.[13]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 19% of patients. The most frequent serious adverse reactions (≥1%) were lung infection (2.3%), pneumonia (1.5%), respiratory failure (1.5%), pneumonitis (1.5%) and abnormal hepatic function (1.5%).[1]

Permanent discontinuation of penpulimab-kcqx due to an adverse reaction occurred in 3.8% of patients.[14,1] Adverse reactions which resulted in permanent discontinuation of penpulimab-kcqx were pleural effusion, herpes zoster disseminated infection, spinal cord compression, transaminase increase, and pemphigoid (0.8% each).[1]

Dosage interruptions of penpulimab-kcqx due to an adverse reaction occurred in 25% of patients.[14,1] Adverse reactions which required dosage interruption in ≥ 1% of patients included abnormal hepatic function, hypothyroidism, pneumonia, and anemia.[1]

If approved, labeling will include the following risks in the Warnings and Precautions section. Similar to dostarlimab-gxly (Jemperli)[15], another PD-1 blocking antibody, labeling will include management for the

risks of severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT) and embryo-fetal toxicity.

5.1 SEVERE AND FATAL IMMUNE-MEDIATED ADVERSE REACTIONS

Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD- L1 blocking antibody. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Similar to dostarlimab-gxly (Jemperli)[15], labeling instructs healthcare providers to monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions, and evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, labeling instructs healthcare providers to initiate appropriate workup to exclude alternative etiologies, including infection. Labeling also instructs healthcare providers to withhold or permanently discontinue penpulimab-kcqx depending on severity, and in general, if penpulimab-kcqx requires interruption or discontinuation, similar to dostarlimab-gxly (Jemperli), recommendations for initiating systemic corticosteroid therapy will likely be communicated in the Warnings and Precautions section of the label for the management of immune-mediated adverse reactions. To increase the prominence of this information and promote mitigation of immune-mediated adverse reactions, a Medication Guide as part of labeling will be included to inform patients regarding the potential risks of immune-mediated adverse reactions. Monitoring and dosage modifications for toxicities to address the safety issues with penpulimab-kcqx will likely be included in the Dosage and Administration section of the label.[1]

Section 5.1 of the draft labeling describes the risk of immune-mediated adverse reactions which include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and other immune-mediated adverse reactions. These immune-mediated adverse reactions are summarized below[1]:

(b) (4)

Section 5.1 of the draft labeling also describes other immune-mediated adverse reactions that were reported in < 1% of patients receiving penpulimab-kcqx.[1]

5.2 INFUSION-RELATED REACTIONS

In clinical studies, 4% (15/372) of patients receiving penpulimab-kcqx were reported with hypersensitivity and anaphylaxis, including three Grade 1 (0.8%) and twelve Grade 2 (3.2%) reactions. Four of the 15 patients required systemic corticosteroids. If penpulimab-kcqx is approved, the labeling will include recommendations (b) (4) (b) (4). Labeling also instructs to interrupt or slow the rate of infusion for mild (b) (4) or moderate (b) (4) infusion-related reactions. For severe (b) (4) or life-threatening (b) (4) infusion-related reactions,

stop infusion and permanently discontinue penpulimab-kcqx. Labeling will include dose modifications in the Dosage and Administration section of the label.[1]

5.3 COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome, have been reported in allogeneic HSCT patients treated with PD-1/L-1 blocking antibody. If approved, this risk will be communicated in the warnings and precautions section of the label.[1]

5.4 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, penpulimab-kcqx can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. The proposed label states to advise pregnant women of the potential risk to a fetus. If approved, healthcare providers should advise females of reproductive potential to use effective contraception during treatment with penpulimab-kcqx and for 4 months after the last dose.[1]

6 Expected Postmarket Use

According to the currently proposed indication, if approved, penpulimab-kcqx will be used in both inpatient and outpatient settings (such as infusion centers). It is expected that oncologists, familiar with the management of toxicities such as severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT and embryo-fetal toxicity, will be the likely prescribers of penpulimab-kcqx.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for penpulimab-kcqx 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 penpulimab-kcqx, 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.

Penpulimab-kcqx is a PD-1 blocking antibody, with the proposed indication for the treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. NPC is an epithelial carcinoma arising from the nasopharyngeal mucosal lining. It has a high propensity to metastasize to distant sites and poses a significant risk for isolated local recurrences after radiation for locally advanced disease. Current treatment relies on both concurrent chemoradiotherapy

with adjuvant chemotherapy or induction chemotherapy followed by concurrent chemoradiation. For patients who have failed first-line platinum-containing chemotherapy and whose disease has relapsed within one year after the chemotherapy regimen, second-line chemotherapy, including gemcitabine, capecitabine, or paclitaxel, may be considered. However, to date, there are no approved drugs for the treatment of patients with metastatic NPC in US. Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease.

Based on the efficacy and safety information currently available, the clinical reviewer stated that penpulimab-kcqx shows clinically meaningful benefit and recommends approval of penpulimab-kcqx using the accelerated approval pathway for the treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[13] The Agency has issued a post-marketing required (PMR) study, which include conducting a multiregional randomized clinical trial and submit progression-free survival (PFS) results that verify and describe the clinical benefit of penpulimab in patients with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[13]

DRM and DO2 have determined that if approved, a REMS is not necessary to ensure the benefits of penpulimab-kcqx outweigh its risks. Penpulimab-kcqx appeared efficacious in its primary outcome of ORR and secondary outcomes of DOR, and its risks can be communicated and managed through labeling.[1,13] The clinical reviewer stated that the durable ORR observed amongst patients treated with penpulimab-kcqx in AK105-202 provides patients with a meaningful option in a treatment space where there is no FDA-approved therapy. An ORR of large magnitude and long duration is an endpoint reasonably likely to predict clinical benefit in metastatic NPC.[13] The most concerning adverse reactions observed with the use of penpulimab-kcqx are risks for severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT and embryo-fetal toxicity, which are the same as in the currently approved PD-1 blocking antibody dostarlimab-gxly (Jemperli).[15] It is expected that oncologists, familiar with the management of these toxicities, will be the likely prescribers of penpulimab-kcqx. The review team concluded the observed safety profile is acceptable when assessed in the context of a life-threatening disease with unmet medical need.[13] None of the PD-1 blocking antibody products 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 penpulimab-kcqx is approved, similar to dostarlimab-gxly (Jemperli), Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with penpulimab-kcqx, as well as information to be included in Patient Counseling Information, and a Medication Guide as part of labeling to inform patients regarding the potential risks.

9 Conclusion & Recommendations

DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of penpulimab-kcqx for the treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. The management of the risks associated with penpulimab-kcqx 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

[1] Draft Prescribing Information for penpulimab-kcqx as currently edited by the FDA, last updated September 2, 2022.

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[13] Division of Oncology Disease 2 (DO2) Assessment Aid (draft) for penpulimab-kcqx, BLA 761258, dated September 22, 2022.

[14] Division of Oncology Disease 2 (DO2). Efficacy and Safety Review Presentation. Mid-Cycle Meeting, dated November 29, 2021.

[15] Jemperli. Prescribing Information (last updated 4/2021).

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/s/

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