CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761352Orig1s000

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	761352
PDUFA Goal Date	February 4, 2025
Nexus TTT #	2024-8591, 2024-8593
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Laura Zendel, Pharm.D.
Review Completion Date	November 26, 2024
Subject	Evaluation of Need for a REMS
Established Name	zenocutuzumab-zbco
Trade Name	Bizengri
Name of Applicant	Merus N.V.
Therapeutic Class	bispecific HER2- and HER3-directed antibody
Formulation(s)	375 mg/18.75 mL (20 mg/mL) vial
Dosing Regimen	zenocutuzumab-zbco 750 mg intravenous infusion every 2 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Bizengri (zenocutuzumab-zbco) is necessary to ensure the benefits outweigh its risks. Merus N.V. submitted a Biologic Licensing Application (BLA) 761352 for zenocutuzumab-zbco with the proposed indications for the treatment of adult patients with advanced unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion following progression with prior systemic therapy (b) (4) (b) (4) and adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion following progression with prior systemic therapy (b) (4) (b) (4) The FDA approved indications will be for the treatment of adults with advanced, unresectable or metastatic NSCLC harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy and adults with advanced, unresectable or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy. The serious risks associated with zenocutuzumab-zbco include infusion-related reactions/hypersensitivity/anaphylactic reactions, interstitial lung disease/pneumonitis, left ventricular dysfunction, and embryo-fetal toxicity. The applicant did not submit a proposed REMS but submitted a risk management plan with routine pharmacovigilance activities.

DRM and Division of Oncology 2 (DO2) agree that a REMS is not necessary to ensure the benefits of zenocutuzumab-zbco outweigh its risks. The efficacy of zenocutuzumab-zbco was supported by the eNRGy study groups F and G. In adult patients with advanced unresectable or metastatic *NRG1* fusion-positive NSCLC, the zenocutuzumab-zbco group had an overall response rate (ORR) of 33% with a median duration of response of 7.4 months. In adult patients with advanced unresectable or metastatic *NRG1* fusion-positive pancreatic adenocarcinoma, the zenocutuzumab-zbco group had an ORR of 40%. DO2 recommends accelerated approval based on the currently available data. The serious risk associated with zenocutuzumab-zbco of embryo-fetal toxicity will be communicated in a boxed warning and in the warnings and precautions section of the label. The other serious risks including infusion-related reactions/hypersensitivity/anaphylactic reactions, interstitial lung disease/pneumonitis, and left ventricular dysfunction will be communicated in the warnings and precautions section of the label. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with zenocutuzumab-zbco.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Bizengri (zenocutuzumab-zbco) is necessary to ensure the benefits outweigh its risks. Merus N.V. submitted a Biologic Licensing Application (BLA) 761352 for zenocutuzumab-zbco with the proposed indications for the treatment of

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

adult patients with advanced unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion following progression with prior systemic therapy [redacted] and adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion following progression with prior systemic therapy [redacted] This application is under review in the Division of Oncology 2 (D02). The applicant did not submit a proposed REMS but submitted a risk management plan with routine pharmacovigilance activities.

2. Background

2.1. Product Information

Bizengri (zenocutuzumab-zbco), a NME, is a bispecific HER2- and HER3-directed antibody, proposed for the treatment of adult patients with advanced unresectable or metastatic NSCLC harboring a *NRG1* gene fusion following progression with prior systemic therapy [redacted] and adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion following progression with prior systemic therapy [redacted] Zenocutuzumab-zbco binds to the extracellular domains of HER2 and HER3 expressed on the surface of cells, including tumor cells, inhibiting HER2:HER3 dimerization and preventing *NRG1* binding to HER3. Zenocutuzumab-zbco is proposed to be supplied as a 375 mg/18.75 mL (20 mg/mL) solution in a single-dose vial. The proposed dosing regimen is zenocutuzumab-zbco 750 mg intravenous infusion every 2 weeks until disease progression or unacceptable toxicity.[b] Zenocutuzumab-zbco is not currently approved in any jurisdiction. Zenocutuzumab-zbco was designated as an orphan product, received fast track designation, and breakthrough therapy. If approved, the indication will be approved under accelerated approval based on overall response rate and duration of response.

2.2. Regulatory History

The following is a summary of the regulatory history for zenocutuzumab-zbco BLA 761352 relevant to this review:

- 07/22/2020: Orphan drug designation granted for treatment of pancreatic cancer
- 12/18/2020: Fast track designation granted for treatment of patients with metastatic solid tumors harboring NRG1 gene fusions (NRG1+ cancer) that have progressed on standard of care therapy

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

- 05/17/2023: Breakthrough therapy designation granted for NRG1+ pancreatic ductal adenocarcinoma
- 07/03/2023: Breakthrough therapy designation granted for NRG1+ NSCLC
- 03/04/2024: BLA 761352 submission for the treatment of adult patients with advanced unresectable or metastatic NSCLC harboring a *NRG1* gene fusion following progression with prior systemic therapy [redacted] (b) (4) and adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion following progression with prior systemic therapy [redacted] (b) (4) [redacted] (b) (4)
- 06/17/2024: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for zenocutuzumab-zbco
- 11/04/2024: Major amendment letter sent to the applicant; PDUFA goal date extended by 3 months to February 4, 2025, due to a major amendment regarding the submission of additional chemistry, manufacturing, and control (CMC) information on October 30, 2024

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

3.1.1. Non-small cell lung cancer

Lung cancer is the third most common cancer and the leading cause of cancer death in the United States.[2,3] Approximately 85% of patients have a group of histological subtypes collectively known as NSCLC, of which lung adenocarcinoma and lung squamous cell carcinoma are the most common subtypes.[4] The primary risk factor for lung cancer is tobacco smoking.[5,6] Second-hand smoking is also a risk factor for lung cancer and other possible risk factors include disease history (chronic obstructive pulmonary disease), cancer history, family history of lung cancer, and exposure to other carcinogens. The estimated number of new cases and the estimated number of deaths of lung and bronchus cancer in the United States in 2024 is 234,580 and 125,070, respectively.[3] The five year relative survival of distant lung and bronchus cancer is 8.9%.[7,c]

NRG1 gene fusions are rare, occurring in approximately 0.3% of patients with NSCLC and most commonly occur in patients with adenocarcinoma histology, particularly invasive mucinous

[c] 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.*

adenocarcinomas.[8,d] While some data suggest NRG1+ NSCLC is more aggressive and less likely to respond to standard frontline treatment, more information is needed before definitive conclusions can be reached.

3.1.2. Pancreatic adenocarcinoma

Pancreatic cancer is the third leading cause of cancer death in the United States.[3] Greater than 90% of pancreatic malignancies are ductal adenocarcinoma and its variants.[9] Risk factors for pancreatic cancer include smoking, elevated body mass index, diabetes, chronic pancreatitis, genetic predisposition, and premalignant tumors of the pancreas. The estimated number of new cases and the estimated number of deaths of pancreatic cancer in the United States in 2024 is 66,440 and 51,750, respectively.[3] *NRG1* fusions are estimated to be below 0.5% of all cases in pancreatic ductal adenocarcinoma.[8,d] The five year relative survival of distant pancreatic cancer is 3.1%.[10,c]

3.2. Description of Current Treatment Options

3.2.1. Non-small cell lung cancer

There are no therapies approved by the FDA specifically targeting NRG1+ NSCLC.[8] Patients with metastatic NRG1+ NSCLC and no other actionable mutations are treated with standard regimens approved for the unselected NSCLC population. First-line treatment for metastatic NSCLC with no targetable mutation include platinum-based chemotherapy with a PD-(L)1 inhibitor. Current guidelines from the National Comprehensive Cancer Network (NCCN) for Non-Small Cell Lung Cancer list a number of systemic agents for subsequent systemic therapy for patients with metastatic NSCLC and disease progression after first-line therapy with immune checkpoint inhibitors plus chemotherapy.[5] Drugs listed in these regimens that are FDA approved for treatment of previously treated advanced unresectable/metastatic NSCLC include docetaxel, pemetrexed, and ramucirumab plus docetaxel.[8]

Taxotere(docetaxel), a microtubule inhibitor, was approved by the FDA for indications including as a single agent for locally advanced or metastatic NSCLC after platinum therapy failure. Labeling includes a boxed warning for toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention.[11] The other serious risks associated with docetaxel in the warnings and precautions section of the label include hematologic effects, enterocolitis and neutropenic colitis, second primary malignancies, cutaneous reactions, neurologic reactions, eye disorders, asthenia, embryo-fetal toxicity, alcohol content, and tumor lysis syndrome. Alimta (pemetrexed), a folate analog metabolic inhibitor, was approved by the FDA for indications including as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy.[12] The serious risks associated with pemetrexed include myelosuppression and increased risk of myelosuppression without vitamin

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

supplementation, renal failure, bullous and exfoliative skin toxicity, interstitial pneumonitis, radiation recall, increased risk of toxicity with ibuprofen in patients with renal impairment, and embryo-fetal toxicity. Cyramza (ramucirumab), a human vascular endothelial growth factor receptor 2 antagonist, was approved by the FDA for indications including in combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy.[13] The serious risks associated with ramucirumab include hemorrhage, gastrointestinal perforations, impaired wound healing, arterial thromboembolic events, hypertension, infusion-related reactions, worsening of pre-existing hepatic impairment, posterior reversible encephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, and embryo-fetal toxicity. Docetaxel, pemetrexed, and ramucirumab were approved in 1996, 2004, and 2014, respectively. These drugs are approved without a REMS.

3.2.2. Pancreatic adenocarcinoma

There are no therapies approved by the FDA specifically targeting NRG1+ pancreatic ductal adenocarcinoma.[8] Patients with NRG1+ pancreatic ductal adenocarcinoma are treated with standard of care chemotherapy, based on survival benefit observed with combination regimens. Treatment of patients with unresectable or metastatic pancreatic ductal adenocarcinoma is palliative. First-line treatment regimens commonly used in the United States include fluoropyrimidine-, oxaliplatin, and irinotecan-based regimens (FOLFIRI and NALIRIFOX) and the combination of gemcitabine and nab-paclitaxel (GNP). Treatment of patients with disease progression is determined by the prior first-line therapy received. Liposomal irinotecan in combination with fluorouracil and leucovorin is the only FDA approved therapy for relapsed/refractory disease. Onivyde (irinotecan liposome), a topoisomerase inhibitor, was approved by the FDA in 2015; indications include in combination with fluorouracil and leucovorin, for the treatment of adult patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.[14] Labeling includes a boxed warning for severe neutropenia and severe diarrhea. The other serious risks associated with irinotecan liposome in the warnings and precautions section of the label include interstitial lung disease (ILD), severe hypersensitivity reaction, and embryo-fetal toxicity. Irinotecan liposome was approved without a REMS.

Please refer to D02 multi-disciplinary review and evaluation (draft) for zenocutuzumab-zbco for a detailed clinical review on treatment armamentarium relevant to the proposed indications.

4. Benefit Assessment

The pivotal trial eNRGy (NCT 02912949) supporting this application for efficacy and safety of zenocutuzumab-zbco consisted of a Phase 2, multicenter, open-label, multi-cohort clinical study.[1,8] In the eNRGy study, group F included adult patients with advanced unresectable or metastatic *NRG1* fusion-positive NSCLC who had disease progression following standard of care treatment for their disease. Patients (N=64) received zenocutuzumab-zbco 750 mg intravenous infusion every 2 weeks until unacceptable toxicity or disease progression. The endpoints included confirmed overall response rate

(ORR) and duration of response (DOR) as determined by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The zenocutuzumab-zbco treatment group had an ORR of 33% (95% CI 22% to 46%). The median DOR was 7.4 months in the zenocutuzumab-zbco group (95% CI 4 to 16.6).

In the eNRGy study, group G included adult patients with advanced unresectable or metastatic *NRG1* fusion-positive pancreatic adenocarcinoma who had disease progression following standard of care treatment. Patients (N=30) received zenocutuzumab-zbco 750 mg intravenous infusion every 2 weeks until unacceptable toxicity or disease progression. The endpoints included confirmed ORR and DOR as determined by BICR according to RECIST v1.1. The zenocutuzumab-zbco treatment group had an ORR of 40% (95% CI 23% to 59%). The percentage of responders with a DOR of ≥ 6 months was 67%.

The clinical reviewer recommended accelerated approval based on the currently available data.[e] The clinical reviewer stated the observed ORR and DOR represent a clinically meaningful treatment effect in patients with previously treated NRG1 fusion-positive NSCLC and pancreatic ductal adenocarcinoma and provide substantial evidence of effectiveness for both settings. The submitted evidence meets the statutory evidentiary standard for accelerated approval of zenocutuzumab-zbco for the treatment of patients with advanced unresectable or metastatic NSCLC or pancreatic ductal adenocarcinoma harboring an NRG1 fusion with disease progression on or after prior systemic therapy.

5. Risk Assessment & Safe-Use Conditions

The safety of zenocutuzumab-zbco was evaluated in a Phase 2 clinical trial eNRGy (NCT 02912949).[1,8,f] The pooled safety population for the serious risks described in labeling included 175 patients with *NRG1* gene fusion positive tumors in the eNRGy study who received zenocutuzumab-zbco 750 mg intravenously every 2 weeks as a single agent until disease progression or unacceptable toxicity. This safety population included 99 patients with NSCLC (group F), 39 patients with pancreatic adenocarcinoma (group G), and 37 patients with other solid tumors (group H). In the pooled safety population, common adverse reactions reported with zenocutuzumab-zbco included diarrhea, musculoskeletal pain, fatigue, nausea, infusion-related reactions, dyspnea, rash, constipation, vomiting, abdominal pain, and edema. The most common Grade 3 or 4 laboratory abnormalities included increased gamma-glutamyltransferase (GGT), decreased hemoglobin, decreased sodium, decreased platelets, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased alkaline phosphatase, decreased magnesium, decreased phosphate, increased activated partial thromboplastin time (aPTT), and increased bilirubin.

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[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.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

In the safety population for patients with unresectable or metastatic NSCLC with *NRG1* gene fusions, 99 patients received zenocutuzumab-zbco. Discontinuation due to an adverse reaction occurred in 3% of the zenocutuzumab-zbco group. Common adverse reactions reported with zenocutuzumab-zbco included diarrhea, musculoskeletal pain, dyspnea, fatigue, cough, rash, infusion-related reactions, decreased appetite, edema, and nausea. In the safety population for patients with unresectable or metastatic pancreatic adenocarcinoma with *NRG1* gene fusions, 39 patients received zenocutuzumab-zbco. Common adverse reactions reported with zenocutuzumab-zbco included diarrhea, musculoskeletal pain, nausea, vomiting, and fatigue.

Five deaths due to a treatment emergent adverse event were reported in the eNRGy study in the pooled safety population.[8] In patients with NSCLC, 2 deaths were due to respiratory failure and 1 death was due to cardiac failure. In patients with pancreatic ductal adenocarcinoma, 1 death was due to respiratory failure and 1 death was due to COVID-19. Per the clinical reviewer's assessment of the deaths, a causal association with zenocutuzumab-zbco cannot be ruled out, however, each case was associated with other contributing factors. Please refer to the D02 multi-disciplinary review and evaluation (draft) for further details related to this analysis.

The serious risks[g] associated with zenocutuzumab-zbco which include infusion-related reactions/hypersensitivity/anaphylactic reactions, ILD/pneumonitis, left ventricular dysfunction, and embryo-fetal toxicity are summarized in the sections below.

5.1. Infusion-Related Reactions/Hypersensitivity/Anaphylactic Reactions

Zenocutuzumab-zbco may cause serious and life-threatening infusion-related reactions, hypersensitivity, and anaphylactic reactions. An adverse reaction of infusion-related reactions occurred in 13% of patients receiving zenocutuzumab-zbco, with all infusion-related reactions reported to be Grade 1 or Grade 2. The median time to onset was 63 minutes from the start of infusion, with a range from 13 minutes to 240 minutes;91% of infusion-related reactions occurred during the first infusion. The proposed label recommends to administer zenocutuzumab-zbco in a setting with emergency resuscitation equipment and staff who are trained to monitor for infusion-related reactions and to administer emergency medications. The proposed label states to monitor patients closely for signs and symptoms of infusion reactions during infusion and for at least 1 hour following completion of first zenocutuzumab-zbco infusion and as clinically indicated. It also states prior to the first zenocutuzumab-zbco infusion, premedicate with a corticosteroid, an H1 antihistamine, and acetaminophen to reduce the risk of infusion-related reactions and that corticosteroid premedication can be used as necessary for

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

subsequent zenocutuzumab-zbco infusions. Recommended premedications are addressed in section 2 of the label.

The proposed label recommends to interrupt zenocutuzumab-zbco infusion in patients with ≤ Grade 3 infusion-related reactions and administer symptomatic treatment as needed and to resume infusion at a reduced rate after resolution of symptoms. It recommends to immediately stop the infusion and permanently discontinue zenocutuzumab-zbco for Grade 4 or life-threatening infusion-related reactions or hypersensitivity/anaphylaxis reactions. Recommendations for management of infusion-related reactions are addressed in section 2 of the label. If approved, these risks will be communicated in the warnings and precautions and dosing and administration sections of the label.

5.2. Interstitial Lung Disease/Pneumonitis

Zenocutuzumab-zbco may cause serious and life-threatening ILD/pneumonitis. An adverse reaction of ILD/pneumonitis occurred in 1.1% of patients receiving zenocutuzumab-zbco, with Grade 2 ILD/pneumonitis reported in 0.6% of patients. The proposed label recommends to monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever) and to immediately withhold zenocutuzumab-zbco in patients with suspected ILD/pneumonitis and administer corticosteroids as clinically indicated. It recommends to permanently discontinue zenocutuzumab-zbco if ILD/pneumonitis ≥ Grade 2 is confirmed. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3. Left Ventricular Dysfunction

Left ventricular ejection fraction (LVEF) decrease has been reported with anti-HER2 therapies. An adverse reaction of Grade 2 LVEF decrease [Grade 2 LVEF decrease (40%-50%; 10 - 19% drop from baseline)] occurred in 2% of patients receiving zenocutuzumab-zbco. In addition, an adverse reaction of cardiac failure without LVEF decrease was reported in 1.7% of patients receiving zenocutuzumab-zbco, with a fatal event reported in one patient. The proposed label states that treatment with zenocutuzumab-zbco has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment. The proposed label recommends before initiating zenocutuzumab-zbco, evaluate LVEF and monitor at regular intervals during treatment as clinically indicated. It recommends for LVEF of less than 45% or less than 50% with absolute decrease from baseline of 10% or greater which is confirmed, to permanently discontinue zenocutuzumab-zbco. It also recommends to permanently discontinue zenocutuzumab-zbco in patients with symptomatic congestive heart failure. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4. Embryo-Fetal Toxicity

Zenocutuzumab-zbco may cause fetal harm based on the mechanism of action of the drug. No clinical data is available with zenocutuzumab-zbco in pregnancy in humans. However, oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death has been reported with HER2-directed antibody during pregnancy in literature reports. Furthermore, animal

studies have demonstrated that inhibition of HER2 and/or HER3 results in impaired embryo-fetal development, including effects on cardiac, vascular and neuronal development, and embryolethality. The risk of embryo-fetal toxicity is proposed to be included in a boxed warning, the warnings and precautions section of the label, and patient information. The proposed label states to advise patients of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting zenocutuzumab-zbco and that effective contraception be used during treatment and for 2 months after the last dose.

6. Expected Postmarket Use

If approved, zenocutuzumab-zbco will primarily be used in both inpatient and outpatient (such as infusion centers) settings. The likely prescribers will be oncologists.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for zenocutuzumab-zbco beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of zenocutuzumab-zbco on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Zenocutuzumab-zbco is a bispecific HER2- and HER3-directed antibody and will be the first targeted agent to be approved for the treatment of adults with advanced, unresectable or metastatic NSCLC harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy and adults with advanced, unresectable or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy. The efficacy of zenocutuzumab-zbco was supported by the eNRGy study groups F and G. In adult patients with advanced unresectable or metastatic *NRG1* fusion-positive NSCLC, the zenocutuzumab-zbco group had an ORR of 33% with a median DOR of 7.4 months. In adult patients with advanced unresectable or metastatic *NRG1* fusion-positive pancreatic adenocarcinoma, the zenocutuzumab-zbco group had an ORR of 40%. The serious risk associated with zenocutuzumab-zbco of embryo-fetal toxicity will be communicated in a boxed warning and in the warnings and precautions section of the label. The other serious risks including infusion-related reactions/hypersensitivity/anaphylactic reactions, ILD/pneumonitis, and left ventricular dysfunction will be communicated in the warnings and precautions section of the label.

Lung cancer is the third most common cancer and the leading cause of cancer death in the United States. Approximately 85% of patients have a group of histological subtypes collectively known as NSCLC. The estimated number of new cases and the estimated number of deaths of lung and bronchus cancer in the United States in 2024 is 234,580 and 125,070, respectively. The five year relative survival of distant lung and bronchus cancer is 8.9%. Pancreatic cancer is the third leading cause of cancer death in the United States. Greater than 90% of pancreatic malignancies are ductal adenocarcinoma and its variants. The estimated number of new cases and the estimated number of deaths of pancreatic cancer in the United States in 2024 is 66,440 and 51,750, respectively. The five year relative survival of distant pancreatic cancer is 3.1%. *NRG1* gene fusions occur in approximately 0.3% of patients with NSCLC and are estimated to be below 0.5% of all cases in pancreatic ductal adenocarcinoma. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with zenocutuzumab-zbco. The clinical reviewer stated the safety profile for zenocutuzumab-zbco is considered acceptable when assessed in the context of a life-threatening disease and these safety concerns will be addressed in the Boxed Warning and Warnings and Precautions section of the label. If approved, based on the efficacy and risks associated with zenocutuzumab-zbco for the treatment of adults with advanced, unresectable or metastatic NSCLC harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy and adults with advanced, unresectable or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy, the DRM and DO2 agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risk can be adequately communicated in labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for zenocutuzumab-zbco to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Proposed prescribing information for zenocutuzumab-zbco as currently edited by FDA, last accessed November 23, 2024.

[2] Olickal T. Division of Risk Management NME review for repotrectinib, November 13, 2023.

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[6] Alexander M, Kim SY, Cheng H. Update 2020: Management of Non-Small Cell Lung Cancer. *Lung*. 2020;198(6):897-907.

[7] Cancer Stat Facts: Lung and Bronchus Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/lungb.html (accessed 2024 October 4)

[8] Bizengri (zenocutuzumab) BLA 761352 multi-disciplinary review and evaluation. Last accessed November 23, 2024.

[9] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Pancreatic Adenocarcinoma (version 3.2024 – August 2, 2024). https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf (accessed 2024 October 4).

[10] Cancer Stat Facts: Pancreatic Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/pancreas.html (accessed 2024 October 4).

[11] Taxotere (docetaxel) package insert. Bridgewater, NJ: Sanofi-aventis U.S. LLC; 2023 January.

[12] Alimta (pemetrexed) package insert. Indianapolis, IN: Lilly USA, LLC; 2022 August.

[13] Cyramza (ramucirumab) package insert. Indianapolis, IN: Eli Lilly and Company; 2022 March.

[14] Onivyde (irinotecan liposome) package insert. Cambridge, MA: Ipsen Biopharmaceuticals, Inc.; 2024 February.

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