CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	761334
PDUFA Goal Date	April 8, 2023
TTT #	2022-769, 2022-772
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
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Review Completion Date	March 28, 2023
Subject	Evaluation of Need for a REMS
Established Name	retifanlimab-dlwr
Trade Name	Zynyz
Name of Applicant	Incyte Corporation
Therapeutic Class	programmed death receptor-1 (PD-1)- blocking antibody
Formulation(s)	500 mg/20 mL vial
Dosing Regimen	retifanlimab-dlwr 500 mg intravenous infusion every 4 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 Zynyz (retifanlimab-dlwr) is necessary to ensure the benefits outweigh its risks. Incyte Corporation submitted a Biologic Licensing Application (BLA) 761334 for retifanlimab-dlwr with the proposed indication for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma. The FDA approved indication will be for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. The serious risks associated with retifanlimab-dlwr include 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 proposed REMS or risk management plan with this application.

DRM and Division of Oncology 3 (DO3) agree that a REMS is not necessary to ensure the benefits of retifanlimab-dlwr outweigh its risks. The efficacy of retifanlimab-dlwr was supported by the POD1UM-201 study, in which the retifanlimab-dlwr group had an objective response rate (ORR) of 52%. DO3 recommends accelerated approval based on the currently available data. The serious risks associated with retifanlimab-dlwr of severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The FDA clinical reviewer stated the safety profile of retifanlimab-dlwr is consistent with the known safety profile of other anti-programmed death receptor-1 (PD-1) antibodies and no new safety signals for this class of drug were identified. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with retifanlimab-dlwr.

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] Zynyz (retifanlimab-dlwr) is necessary to ensure the benefits outweigh its risks. Incyte Corporation submitted a Biologic Licensing Application (BLA) 761334 for retifanlimab-dlwr with the proposed indication for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma.[1] The FDA approved indication will be for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. This application was approved by the Division of Oncology 3 (DO3) on March 22, 2023. The applicant did not submit a proposed REMS or risk management plan with this application.

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

2. Background

2.1. Product Information

Zynyz (retifanlimab-dlwr), a new molecular entity (NME), is a programmed death receptor-1 (PD-1)-blocking antibody, proposed for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma. The FDA approved indication will be for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. Retifanlimab-dlwr injection is supplied as a 500 mg/20 mL solution in a single-dose vial. The approved dosing regimen is retifanlimab-dlwr 500 mg administered as an intravenous infusion over 30 minutes every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months.[b] Retifanlimab-dlwr was approved by the FDA on March 22, 2023. Retifanlimab-dlwr received fast track designation and was designated as an orphan product. The indication was approved under accelerated approval based on tumor response rate and duration of response.

2.2. Regulatory History

The following is a summary of the regulatory history for retifanlimab-dlwr BLA 761334 relevant to this review:

- 10/26/2020: Orphan drug designation granted
- 11/06/2020: Fast track designation granted
- 08/08/2022: BLA 761334 submission for the treatment of adult (b) (4) patients (b) (4) with metastatic or recurrent locally advanced Merkel cell carcinoma received
- 11/21/2022: 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 retifanlimab-dlwr.
- 3/22/2023: FDA approved retifanlimab-dlwr, BLA 761334, for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma without a REMS.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Merkel cell carcinoma is a rare and aggressive neuroendocrine carcinoma of the skin.[2,3] Risk factors include sun exposure, older age, male gender, Caucasian ethnicity, immunosuppression, and Merkel cell

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

polyomavirus infection.[3,4] There are approximately 2488 cases of Merkel cell carcinoma in the United States each year.[c] Patients with Merkel cell carcinoma may develop metastatic disease, with approximately one-third of patients developing distant metastasis. The five-year relative survival rate of localized, regional, and distant Merkel cell carcinoma is 75%, 61%, and 24%, respectively.[5,d]

3.2. Description of Current Treatment Options

Current guidelines from the National Comprehensive Cancer Network (NCCN) for Merkel Cell Carcinoma list immunotherapy including avelumab, pembrolizumab, and nivolumab and chemotherapy for systemic therapy for metastatic or unresectable disease.[3] Keytruda (pembrolizumab), a PD-1 blocking antibody, was approved by the FDA for indications including the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[6] The indication for the treatment of Merkel cell carcinoma was approved under accelerated approval based on tumor response rate and durability of response. Bavencio (avelumab), a programmed death ligand-1 (PD-L1) blocking antibody, was approved by the FDA for indications including the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma.[7] The indication for the treatment of Merkel cell carcinoma was approved under accelerated approval based on tumor response rate and duration of response. Pembrolizumab and avelumab were approved in 2014 and 2017, respectively.

The serious risks associated with pembrolizumab include severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), increased mortality in patients with multiple myeloma when Keytruda is added to a thalidomide analogue and dexamethasone, and embryo-fetal toxicity. The serious risks associated with avelumab include severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT, major adverse cardiovascular events, and embryo-fetal toxicity. Pembrolizumab and avelumab do not have a boxed warning in their respective labels and did not require a REMS.

4. Benefit Assessment

The pivotal trial POD1UM-201 (NCT 03599713) supporting this application for efficacy and safety consisted of a Phase 2, open-label, multiregional, single-arm study in patients with metastatic or recurrent locally advanced Merkel cell carcinoma who had not received prior systemic therapy for their advanced disease.[1,4] Patients (N=65) received retifanlimab-dlwr intravenously every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months. The primary endpoint was objective

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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.*

response rate (ORR). Secondary endpoints included duration of response (DOR). The retifanlimab-dlwr treatment group had an ORR of 52% (95% CI 40% to 65%). In 34 patients who experienced an objective response, the DOR was ≥ 6 months for 76% of patients and ≥ 12 months for 62% of patients. The FDA clinical reviewer recommended accelerated approval based on the currently available data.[e]

5. Risk Assessment & Safe-Use Conditions

The safety of retifanlimab-dlwr was evaluated in a Phase 2 clinical trial POD1UM-201 (NCT 03599713).[1,4,f] In the safety population, 105 patients received retifanlimab-dlwr. However, the safety population for the serious risks in section 5.1 to section 5.4 below included 105 patients with Merkel cell carcinoma in the POD1UM-201 study and 335 patients with other solid tumors. Discontinuation due to an adverse reaction occurred in 11% of the retifanlimab-dlwr group. Common adverse reactions reported with retifanlimab-dlwr included fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia, and nausea.

Three deaths due to a treatment emergent adverse event were reported in the POD1UM-201 study in the retifanlimab-dlwr group.[4] The Applicant indicated that the causes of death due to a treatment emergent adverse events included asthenia, concomitant disease progression of chronic lymphocytic leukemia, and acute respiratory failure.

The serious risks[g] associated with retifanlimab-dlwr which include severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity are summarized in the sections below.

5.1. Severe and Fatal Immune-Mediated Adverse Reactions

Section 5.1 of the labeling describes the risk of severe and fatal immune-mediated adverse reactions which include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis,

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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.*

[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.

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.

The label recommends monitoring for symptoms and signs of immune-mediated adverse reactions. It states to evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment, in cases of suspected immune-mediated adverse reactions to initiate appropriate workup to exclude alternative etiologies including infection, and to institute medical management promptly, including specialty consultation as appropriate. Dose modifications for retifanlimab-dlwr are addressed in section 2 of the label. The label recommends to withhold or permanently discontinue retifanlimab-dlwr depending on the severity of immune-mediated adverse reactions. It also contains recommendations for supportive care of immune-mediated adverse reactions including administering systemic corticosteroids if interruption or discontinuation of retifanlimab-dlwr is required. Section 5.1 of the labeling also contains management guidelines for adverse reactions that do not necessarily require systemic steroids (endocrinopathies, dermatologic reactions) and these recommendations are summarized below. These risks will be communicated in the warnings and precautions section of the label.

Immune-mediated pneumonitis

An adverse event of immune-mediated pneumonitis occurred in 3% of patients receiving retifanlimab-dlwr, with Grade 2 immune-mediated pneumonitis reported in 1.4% of patients, Grade 3 immune-mediated pneumonitis reported in 0.9% of patients, and fatal immune-mediated pneumonitis reported in 0.2% of patients

Immune-mediated colitis

An adverse event of immune-mediated colitis occurred in 1.6% of patients receiving retifanlimab-dlwr, with Grade 2 immune-mediated colitis reported in 0.7% of patients, Grade 3 immune-mediated colitis reported in 0.2% of patients, and Grade 4 immune-mediated colitis reported in 0.2% of patients.

Immune-mediated hepatitis

An adverse event of immune-mediated hepatitis occurred in 3% of patients receiving retifanlimab-dlwr, with Grade 2 immune-mediated hepatitis reported in 0.5% of patients, Grade 3 immune-mediated hepatitis reported in 2.3% of patients, and Grade 4 immune-mediated hepatitis reported in 0.2% of patients.

Immune-mediated endocrinopathies

An adverse event of adrenal insufficiency occurred in 0.7% of patients receiving retifanlimab-dlwr, with Grade 2 adrenal insufficiency reported in 0.2% of patients and Grade 3 adrenal insufficiency reported in 0.5% of patients. The label recommends for Grade 2 or higher adrenal insufficiency to initiate symptomatic treatment per institutional guidelines including hormone replacement as clinically indicated and to withhold or permanently discontinue retifanlimab-dlwr depending on severity.

An adverse event of hypophysitis occurred in 0.5% of patients receiving retifanlimab-dlwr, with Grade 2 hypophysitis reported in 0.5% of patients. The label recommends initiating hormone replacement as clinically indicated and to withhold or permanently discontinue retifanlimab-dlwr depending on severity.

An adverse event of thyroiditis occurred in 0.7% (all Grade 1) of patients receiving retifanlimab-dlwr. An adverse event of hypothyroidism occurred in 10% of patients receiving retifanlimab-dlwr, with Grade 2 hypothyroidism reported in 4.8% of patients. In addition, an adverse event of hyperthyroidism occurred in 6% of patients receiving retifanlimab-dlwr, with Grade 2 hyperthyroidism reported in 2.5% of patients. The label recommends initiating hormone replacement or medical management of hyperthyroidism as clinically indicated and to withhold or permanently discontinue retifanlimab-dlwr depending on severity.

Section 5.1 of the labeling also states that Type 1 diabetes mellitus which can present as diabetic ketoacidosis may occur with retifanlimab-dlwr. An adverse event of Type 1 diabetes mellitus occurred in 0.2% of patients receiving retifanlimab-dlwr, with Grade 3 Type 1 diabetes mellitus reported in 0.2% of patients. The label recommends monitoring patients for hyperglycemia or other signs and symptoms of diabetes, to initiate treatment with insulin as clinically indicated, and to withhold retifanlimab-dlwr depending on severity.

Immune-mediated nephritis with renal dysfunction

An adverse event of immune-mediated nephritis occurred in 1.6% of patients receiving retifanlimab-dlwr, with Grade 2 immune-mediated nephritis reported in 0.5% of patients, Grade 3 immune-mediated nephritis reported in 0.7% of patients, and Grade 4 immune-mediated nephritis reported in 0.5% of patients.

Immune-mediated dermatologic adverse reactions

Section 5.1 of the labeling states that immune-mediated rash or dermatitis may occur with retifanlimab-dlwr. In addition, bullous and exfoliative dermatitis, including Stevens Johnson Syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis have been reported with PD-1/PD-L1 blocking antibodies.

An adverse event of immune-mediated skin reactions occurred in 8% of patients receiving retifanlimab-dlwr, with Grade 2 immune-mediated skin reactions reported in 7% of patients, and Grade 3 immune-mediated skin reactions reported in 1.1% of patients. The label states that topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes and to withhold or permanently discontinue retifanlimab-dlwr depending on severity.

Other immune-mediated adverse reactions

Section 5.1 of the labeling also describes other immune-mediated adverse reactions that were reported in < 1% of patients receiving retifanlimab-dlwr or other PD-1/PD-L1 blocking antibodies.

5.2. Infusion-Related Reactions

An adverse reaction of infusion-related reactions occurred in 0.2% (1/440, Grade 3) of patients receiving retifanlimab-dlwr. The label recommends monitoring patients for signs and symptoms of infusion

related reactions and to interrupt or slow the rate of infusion or permanently discontinue retifanlimab-dlwr based on severity of reaction. The label also states to consider premedication with an antipyretic and/or an antihistamine for patients who have had previous systemic reactions to infusions of therapeutic proteins. This risk will be communicated in the warnings and precautions section of the label.

5.3. Complications of Allogeneic HSCT

Allogeneic HSCT complications, including hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome, may occur in allogeneic HSCT patients treated with PD-1/PD-L1 receptor blocking antibody. The label states to follow patients closely for evidence of transplant-related complications and intervene promptly. The label also states to consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT. This risk will be communicated in the warnings and precautions section of the label.

5.4. Embryo-Fetal Toxicity

Retifanlimab-dlwr may cause fetal harm based on the mechanism of action of the drug. Inhibition of the PD-1/PD-L1 pathway in animal studies has been reported to increase the risk of immune-mediated rejection of the developing fetus and fetal death. No clinical data is available with retifanlimab-dlwr in pregnancy in humans. The risk of embryo-fetal toxicity will be included in a Medication Guide and the warnings and precautions section of the label. The label states to advise women of the potential risk to a fetus. The label recommends in females of reproductive potential to verify pregnancy status before starting retifanlimab-dlwr and that effective contraception be used during treatment and for 4 months after the last dose.

6. Expected Postmarket Use

Retifanlimab-dlwr 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 retifanlimab-dlwr beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of retifanlimab-dlwr on the basis of the efficacy and safety information currently available. At the time of documentation of this review, retifanlimab-dlwr was approved on March 22, 2023. The FDA approved indication is for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. (b) (4) The indication is approved under accelerated approval based on tumor response rate and duration of response.

The efficacy of retifanlimab-dlwr was supported by the POD1UM-201 study, in which the retifanlimab-dlwr group had an ORR of 52%. The clinical review noted that the POD1UM study demonstrated a clinically meaningful and durable response rate and the submitted data meets the evidentiary standards for accelerated approval in the proposed patient population. The serious risks associated with retifanlimab-dlwr of severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The FDA clinical reviewer stated the safety profile of retifanlimab-dlwr is acceptable for treatment of a serious and life-threatening condition, is consistent with the known safety profile of other anti-PD-1 antibodies and no new safety signals for this class of drug were identified.

Merkel cell carcinoma is a rare and aggressive neuroendocrine tumor of the skin. There are approximately 2488 cases of Merkel cell carcinoma in the United States each year. Patients with Merkel cell carcinoma may develop metastatic disease, with approximately one-third of patients developing distant metastasis. The five-year relative survival rate of localized, regional, and distant Merkel cell carcinoma is 75%, 61%, and 24%, respectively. Based on the POD1UM-201 study, retifanlimab-dlwr offers an additional treatment option to adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with retifanlimab-dlwr. Based on the efficacy and risks associated with retifanlimab-dlwr for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma, the DRM and DO3 agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risks 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 retifanlimab-dlwr to ensure the benefits outweigh the risks.

10. Appendices

10.1. References

[1] Proposed prescribing information for retifanlimab-dlwr as currently edited by FDA, last accessed March 18, 2023.

[2] Redd, N. Division of Risk Management NME review for avelumab, February 21, 2017.

[3] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Merkel Cell Carcinoma (version 2.2022 – March 24, 2022). https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf (accessed 2023 March 20).

[4] Zynyz (retifanlimab-dlwr) multi-disciplinary review and evaluation. Accessed March 18, 2023.

[5] Survival Rates for Merkel Cell Carcinoma. https://www.cancer.org/cancer/merkel-cell-skin-cancer/detection-diagnosis-staging/survival-rates.html (accessed 2023 March 20)

[6] Keytruda (pembrolizumab) package insert. Whitehouse Station, NJ: Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc., 2023 January.

[7] Bavencio (avelumab) package insert. New York, NY: EMD Serono, Inc. and Pfizer Inc., 2022 July.

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