Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Retifanlimab-dlwr (Zynyz®)	MP-RX-FP-138-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Retifanlimab-dlwr (Zynyz®),* a programmed death receptor-1 (PD-1)–blocking antibody approved by the Food and Drug Administration (FDA) for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma.

Background Information

Merkel cell carcinoma (MCC) is an aggressive and rare type of skin cancer with the potential to spread to other parts of the body. Around 60% of MCC tumors occur in men. In the United States, approximately 2,500 new cases are diagnosed each year as of 2015. The incidence rate of MCC in the general U.S. population is about 0.7 cases per 100,000 individuals, but this rate significantly rises to approximately 9.8 cases per 100,000 individuals in those aged over 85 years.

Retifanlimab-dlwr (Zynyz®), is a type of medication known as a programmed death receptor-1 (PD-1)-blocking antibody. It works by binding to the PD-1 receptor, thereby obstructing the interaction between PD-L1 and PD-L2. This interference enhances the activity of T-cells, leading to a suppression of T-cell proliferation and cytokine production. Moreover, in certain tumors, there is an increased expression of PD-1 ligands, which when activated, can impede the active surveillance of tumors by T-cells.

The prescribing information for Zynyz includes important warnings and precautions:

1. Immune-Mediated Adverse Reactions: These reactions, which can be severe or fatal, may affect various organ systems including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, and solid organ transplant rejection. Early detection and management are crucial, necessitating monitoring of liver enzymes, creatinine, and thyroid function both initially and periodically during treatment. Depending on the severity, Zynyz may need to be withheld or permanently discontinued, with corticosteroids administered as necessary.
2. Infusion-Related Reactions: These reactions may occur during the infusion process and may require interruption, slowing of infusion rate, or permanent discontinuation of Zynyz based on their severity.
3. Complications of Allogeneic HSCT: Patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) either before or after receiving treatment with a PD-1/PD-L1–blocking antibody like Zynyz may experience fatal or serious complications.
4. Embryo-Fetal Toxicity: Zynyz has the potential to cause harm to a fetus, and therefore, females of reproductive potential must be advised of this risk and instructed to use effective contraception.

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Retifanlimab-dlwr (Zynyz®) received accelerated approval from the U.S. Food and Drug Administration on March 22, 2023, for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC), based on the single-arm Pod1um-201 trial in which 65 chemotherapy-naïve individuals with metastatic or recurrent locally advanced MCC and treated with Zynyz had complete and partial response rates of 18% and 34% respectively. Serious adverse reactions occurred in 22% of individuals with the most common being fatigue, arrhythmia, and pneumonitis.

NCCN added a 2A recommendation for the use in locally advanced or metastatic squamous carcinoma of the anal cancer as monotherapy post platinum-based therapy.

Definitions and Measures

- Merkel cell carcinoma: A rare, aggressive skin cancer.
- Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- Programmed death (PD)-1: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. Examples of FDA approved PD-1 inhibitors include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab)
- Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1 on their surface, which helps them to avoid immune attacks. Examples of FDA approved PD-L1 inhibitors include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).

Approved Indications

A. Treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma.

This indication was granted under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Other Uses

i. Locally advanced or metastatic squamous anal carcinoma (NCCN 2A).

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9345	Injection, retifanlimab-dlwr, 1 mg [Zynyz]

ICD-10	Description
C4A.0-C4A.9	Merkel cell carcinoma
C17.0-C17.9	Malignant neoplasm of small intestine
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0 – C21.8	Malignant neoplasm of anus and anal canal

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Retifanlimab-dlwr (Zynyz®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of *Merkel Cell Carcinoma*; **AND**
ii. Individual has metastatic or recurrent locally advanced disease not amenable to surgery or radiation (NCCN 2A); **AND**
iii. Individual is using as monotherapy; **AND**
iv. Has not received treatment with an anti-PD-1 or PD-L1 agent.

OR

v. Individual is using as a single agent; **AND**
    A. Individual is using for one of the following disease states:

1. Colon Cancer (NCCN 2A); **OR**
2. Rectal Cancer (NCCN 2A); **OR**
3. Small Bowel Adenocarcinoma (NCCN 2A); **OR**

B. Individual has one of the following mutations**:**
1. Deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]; **OR**
2. Polymerase epsilon/delta [POLE/POLD1] with ultra-hypermutated phenotype (e.g. TMB > 50 mut/MB);

OR

vi. Individual has a diagnosis of Endometrial Carcinoma; **AND**
A. Individual is using as second-line subsequent therapy; **AND**
B. Individual has recurrent microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors; **AND**
C. Individual has not previously used Retifanlimab-dlwr;

OR

vii. Individual has a diagnosis of anal carcinoma (Label, NCCN 2A); **AND**
A. Individual is using in one of the following ways:
1. Individual is using as monotherapy; **AND**
2. Individual is using due to disease progression on or after platinum-based chemotherapy; **AND**
3. Individual has locally recurrent or metastatic squamous cell carcinoma of the anal canal; **AND**
4. Individual is using as second line and subsequent therapy; AND
5. Individual has not received prior treatment with an anti-PD-1 or PD-L1 agent;

OR

6. Individual is using in combination with paclitaxel and carboplatin; **AND**
7. Individual is using as first-line treatment; **AND**
8. Individual has inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Retifanlimab-dlwr (Zynyz®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen and the maximum duration of therapy has not been exceeded. The following information should be submitted for reauthorization:
A. A current oncology note documenting the patient's response to treatment showing no progression of disease.

B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

ii. The maximum duration of therapy for Retifanlimab-dlwr (Zynyz®) for patients with metastatic or recurrent locally advanced Merkel cell carcinoma is 24 months.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months

ii. Reauthorization Approval Duration: Up to 6 months (until the maximum duration of therapy of 24 months has been reached).

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Zynyz (retifanlimab-dlwr) may not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Policy Name	Policy Number	Scope
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Drug	Recommended Dosing Schedule	Limit
Retifanlimab-dlwr (Zynyz®) 500 mg/20 mL (25 mg/mL) SDV	500 mg i.v. every 4 weeks (28 days) until disease progression, unacceptable toxicity, or up to 24 months.	1 vial every 28 days
Exceptions		
• Immune mediated adverse reactions can occur. Monitoring of liver enzymes, creatinine, and thyroid function is recommended at baseline and periodically during treatment.		

Reference Information

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 29, 2024.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
4. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Updated periodically. Accessed on April 18, 2023.
    a. Merkel Cell Carcinoma. V1.2024. Revised January 29, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 11/20/2025	Add 2A recommendations for use in colon, rectal, and small bowel cancers in those with either dMMR/MSI-H or POLE/POLD1 mutations. Coding Reviewed: Added ICD-10-CM C17.0-C20. Update criteria for use in anal carcinoma due to FDA approvals as a single agent and in combination with carboplatin and paclitaxel. Also included NCCN 2A updates. Addition of Endometrial carcinoma criteria.	12/3/2025	12/11/2025
Annual Review 12/26/2024	Add 2A recommendation from NCCN for locally advanced or metastatic squamous carcinoma of the anal canal (SCAC). Updated quantity limits table to add dosage form and strength, and immune mediated reactions warning per FDA label. Wording and formatting changes. Coding Reviewed: Added ICD-10-CM C21.0-C21.8.	3/20/2025	4/2/2025
Policy Inception 01/29/2024	New Medical Policy creation	4/18/2024	6/28/2024