Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Zolbetuximab-clzb (Vyloy)	MP-RX-FP-162-24	☒ 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 Zolbetuximab-clzb (Vyloy®), a claudin 18.2-directed cytolytic antibody approved by the Food and Drug Administration (FDA) in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.

The VENTANA CLDN18 (43-14A) RxDx Assay (Ventana Medical Systems, Inc./Roche Diagnostics) has been approved by the FDA as a companion diagnostic device to identify patients with gastric or GEJ adenocarcinoma who may be eligible for treatment with zolbetuximab.

Background Information

Zolbetuximab-clzb is a claudin 18.2 (CLDN18.2)-directed cytolytic antibody that targets and depletes CLDN18.2-positive cells through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Preclinical studies have shown that combining zolbetuximab-clzb with chemotherapy significantly enhances antitumor activity in CLDN18.2-expressing mouse tumor models compared to either treatment alone, demonstrating its potential as a targeted therapy.

The efficacy of zolbetuximab-clzb was demonstrated in two pivotal randomized, double-blind, multicenter clinical trials: SPOTLIGHT (NCT03504397) and GLOW (NCT03653507). These trials enrolled patients with CLDN18.2-positive advanced, unresectable, or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. In both trials, CLDN18.2 positivity (defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining) was determined by immunohistochemistry on gastric or GEJ tumor tissue specimens from all patients with the VENTANA CLDN18 (43-14A) RxDx Assay. Progression-free survival (PFS), assessed using RECIST v1.1 criteria by an independent review committee, served as the primary efficacy endpoint for both studies, with overall survival (OS) as a key secondary endpoint.

In the SPOTLIGHT trial, 565 patients were randomized 1:1 to receive either zolbetuximab-clzb with mFOLFOX6 chemotherapy or placebo with mFOLFOX6 chemotherapy. The zolbetuximab-clzb arm achieved a median PFS of 10.6 months (95% CI: 8.9, 12.5) versus 8.7 months (95% CI: 8.2, 10.3) in the placebo arm (HR 0.751 [95% CI: 0.598, 0.942]; 1-sided p-value = 0.0066). Median OS was 18.2 months (95% CI: 16.4, 22.9) compared to 15.5 months (95% CI: 13.5, 16.5) in the placebo arm (HR 0.750 [95% CI: 0.601, 0.936]; 1-sided p-value = 0.0053).

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In the GLOW trial, 507 patients were similarly randomized to receive zolbetuximab-clzb with CAPOX chemotherapy or placebo with CAPOX chemotherapy. The median PFS for the zolbetuximab-clzb group was 8.2 months (95% CI: 7.5, 8.8) versus 6.8 months (95% CI: 6.1, 8.1) in the placebo group (HR 0.687 [95% CI: 0.544, 0.866]; 1-sided p-value = 0.0007). Median OS was 14.4 months (95% CI: 12.3, 16.5) in the zolbetuximab-clzb arm compared to 12.2 months (95% CI: 10.3, 13.7) in the placebo arm (HR 0.771 [95% CI: 0.615, 0.965]; 1-sided p-value = 0.0118).

The safety profile of zolbetuximab-clzb was extensively evaluated. In SPOTLIGHT, serious adverse reactions (≥2%) included vomiting, nausea, neutropenia, febrile neutropenia, diarrhea, intestinal obstruction, pyrexia, pneumonia, respiratory failure, pulmonary embolism, decreased appetite, and sepsis. In GLOW, the most common serious adverse reactions (≥2%) were vomiting, nausea, decreased appetite, thrombocytopenia, upper gastrointestinal hemorrhage, diarrhea, pneumonia, pulmonary embolism, and pyrexia.

The recommended dosing regimen for zolbetuximab-clzb includes an initial intravenous dose of 800 mg/m², followed by maintenance doses of either 600 mg/m² every three weeks or 400 mg/m² every two weeks, in combination with fluoropyrimidine- and platinum-based chemotherapy.

The Warnings and Precautions section of the product label highlights important safety considerations, including the risk of hypersensitivity reactions, such as severe anaphylaxis and potentially fatal infusion-related reactions. Patients should be closely monitored during the infusion and for at least two hours afterward to detect and manage adverse events promptly. Additionally, severe nausea and vomiting have been reported, and premedication with antiemetics is recommended prior to each infusion to mitigate these effects. Therapy may need to be interrupted or discontinued based on the severity of these reactions.

Approved Indications

Vyloy is approved by the FDA to be used in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.

Other Uses

None

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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
J3590	Unclassified biologics (Vyloy)
C9399	Unclassified drugs or biologicals (Vyloy)
J9999	Not otherwise classified, antineoplastic drugs (Vyloy)

ICD-10	Description
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified

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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.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Zolbetuximab-clzb (Vyloy®)

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 gastric or gastroesophageal junction adenocarcinoma; **AND**
ii. Individual's adenocarcinoma is either
    A. Locally advanced unresectable; **OR**
    B. Metastatic

AND

iii. The tumor is human epidermal growth factor receptor 2 (HER2)-negative; **AND**
iv. The tumor is claudin (CLDN) 18.2 positive as determined by an FDA-approved test (VENTANA CLDN18 (43-14A) RxDx Assay (Ventana Medical Systems, Inc./Roche Diagnostics)

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Zolbetuximab-clzb (Vyloy®) 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. 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.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

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D. Conditions Not Covered

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

Requests for Zolbetuximab-clzb (Vyloy®) may not be approved when the above criteria 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.

Drug	Recommended Dosing Schedule
Zolbetuximab-clzb (Vyloy®) 100 mg lyophilized powder in a single-dose vial	IV Infusion: 800 mg/m2 followed by 600 mg/m2 every 3 weeks or 400 mg/m2 every 2 weeks.
Exceptions	
None	

Reference Information

1. Astellas Pharma US, Inc. VYLOY (zolbetuximab injection, powder, for suspension) [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc.; 2024.
2. U.S. Food and Drug Administration. FDA approves zolbetuximab-clzb with chemotherapy for gastric or gastroesophageal junction adenocarcinoma. Published October 18, 2024. Accessed November 12, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zolbetuximab-clzb-chemotherapy-gastric-or-gastroesophageal-junction-adenocarcinoma

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3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.

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.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	New Medical Policy Creation	12/9/2024	12/17/2024

Revised: 10/30/2024