Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Margetuximab-cmkb (Margenza®)	MP-RX-FP-56-23	☒ 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 *Margetuximab-cmkb (Margenza®),* a HER2/neu receptor antagonist approved by the Food and Drug Administration (FDA) in combination with chemotherapy for the treatment of adult patients with metastatic HER2- positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Background Information

Breast cancer is a type of tumor comprised of malignant (cancerous) cells that start to grow in the breast and may spread (metastasize) to surrounding tissues and other areas of the body (American Cancer Society, 2016). Breast cancer is commonly treated by various modalities which include combinations of surgery, radiation therapy, chemotherapy and hormone therapy (National Cancer Institute, 2019). The prognosis and selection of therapies can be affected by clinical and pathologic features of the tumor. One of these includes the human epidermal growth factor receptor 2 gene ERBB2 which is commonly referred to as HER2. Other names for this gene include NEU, Her-2, HER-2/neu and c-erb B2. Initially the HER2 gene was detected in frozen breast tumor samples. Amplification of the HER2 gene was later correlated to overexpression of protein levels in samples of breast cancer.

Approximately 276,000 patients are diagnosed with invasive breast cancer each year, with approximately one in five cases being classified as HER-2 positive.

Margenza may lead to reductions in left ventricular ejection fraction. Exposure to Margenza during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Margenza in invasive and inflammatory breast cancer as third-line therapy and beyond in combination with chemotherapy for HER2-positive disease.

There is an update to the SOPHIA trial (Rugo et. al. 2021) for final overall survival (OS) results looking at margetuximab versus trastuzumab in those with previously treated with HER2 positive advance breast cancer. The abstract at this time states Margetuximab safety was comparable with trastuzumab; however, final overall OS analysis did not demonstrate margetuximab advantage over trastuzumab (Rugo et. al. 2022).

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Definitions and Measures

- HER2 testing (adapted from American Society of Clinical Oncology/College of American Pathologists):
  - Positive HER2:
    - IHC 3+ based on circumferential membrane staining that is complete, intense. (Observed in a homogeneous and contiguous population and within > 10% of the invasive tumor cells).
    - ISH positive based on:
      - Single-probe average HER2 copy number ≥ 6.0 signals/cell (Observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells. By counting at least 20 cells within the area)
      - Dual-probe HER2/CEP 17 ratio ≥ 2.0* with an average HER2 copy number ≥ 4.0 signals/cell
      - Dual-probe HER2/CEP17 ratio ≥ 2.0* with an average HER2 copy number < 4.0 signals/cell
      - Dual-probe HER2/CEP17 ratio < 2.0* with an average HER2 copy number ≥ 6.0 signals/cell
  - Equivocal HER2:
    - IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells.
    - ISH equivocal based on:
      - Single-probe average HER2 copy number ≥ 4.0 and < 6.0 signals/cell
      - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 4.0 signals/cell
  - Negative HER2 if a single test (or both tests) performed show:
    - IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells
    - IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells
    - ISH negative based on:
      - Single-probe average HER2 copy number < 4.0 signals/cell
      - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell
- 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.
- Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.
- Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

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- Refractory Disease: Illness or disease that does not respond to treatment.

Approved Indications

Margenza, in combination with chemotherapy, is approved by the FDA for the treatment of:

A. Adult patients with metastatic HER2- positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Other Uses

See Background section above.

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
J9353	Injection, margetuximab-cmkb, 5 mg [Margenza]

ICD-10	Description
C50.011-C50.929	Malignant neoplasm of breast
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.92	Lobular carcinoma in situ of breast
Z85.3	Personal history of malignant neoplasm of breast
Z17.0	Estrogen receptor positive status (ER+)

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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.

Margetuximab-cmkb (Margenza®)

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 metastatic HER2-positive (HER2+) breast cancer (NCCN 1) confirmed by *one* of the following:
   A. Immunohistochemistry (IHC) is 3 +;
   OR
   B. In situ hybridization (ISH) positive;

AND

ii. Individual has had at least two or more prior anti-HER2 therapies, and at least one in the metastatic setting (Label, NCCN 2A);

AND

iii. Individual is using in combination with chemotherapy, capecitabine, eribulin, gemcitabine, or vinorelbine (NCCN 2A; Rugo 2021).

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Margetuximab-cmkb (Margenza®) 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 an 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):

i. Requests for Margetuximab-cmkb (Margenza®) 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	Recommended Treatment Duration
Margetuximab-cmkb (Margenza®)	15 mg/kg i.v.every 3 weeks (21-day cycle)	Until disease progression or unacceptable toxicity.
Exceptions		
None		

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 11, 2023.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
5. Margenza (margetuximab-cmkb) intravenous infusion [product information]. Rockville, MD: MacroGenics; December 2020.

6. NCCN Clinical Practice Guidelines in Oncology™. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 11, 2023
    a. Breast Cancer. V4.2022. Revised June 21, 2022.
7. Rugo HS, Im SA, Cardoso F, et al. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2021 Apr 1;7(4):573-584. Available at: https://jamanetwork.com/journals/jamaoncology/fullarticle/2775599 Accessed January 11, 2023.
8. Rugo HS, Im SA, Cardoso F, Cortes J, e.al; SOPHIA Study Group. Margetuximab Versus Trastuzumab in Patients With Previously Treated HER2-Positive Advanced Breast Cancer (SOPHIA): Final Overall Survival Results From a Randomized Phase 3 Trial. Treated HER2-Positive Advanced Breast Cancer (SOPHIA): Final Overall Survival Results From a Randomized Phase 3 Trial. J Clin Oncol. 2022 Nov 4:JCO2102937. doi: 10.1200/JCO.21.02937. Online ahead of print. Accessed January 11, 2023.

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	MPCC Approval Date
Annual Review. 7/9/2024	Add therapeutic alternatives section. Wording and formatting changes. Coding reviewed: No changes.	2/24/2025	3/6/2025
Select Review 2/15/2024	Update statement for 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.	3/25/2024	5/9/2024
Policy Inception 7/9/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023