Medical Drug Clinical Criteria

Subject:	Margenza (margetuximab-cmkb)		
Document #:	CC-0186	**Publish Date:**	04/01/2025
Status:	Revised	**Last Review Date:**	02/21/2025

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Overview

This document addresses the use of Margenza (margetuximab-cmkb) injection. Margenza is a HER2/neu receptor antagonist FDA approved, 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.

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).

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*
    - 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

*(Observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells. By counting at least 20 cells within the area)

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.

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

Clinical Criteria

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.

Margenza (margetuximab-cmkb)

Requests for Margenza (margetuximab-cmkb) may be approved if the following criteria are met:

I. Individual has a diagnosis of metastatic HER2-positive (HER2+) breast cancer 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).

Requests for Margenza (margetuximab-cmkb) may not be approved when the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

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

ICD-10 Diagnosis

C50.011-C50.929	Malignant neoplasm of breast
C79.81	Secondary malignant neoplasm of breast
Z85.3	Personal history of malignant neoplasm of breast

Document History

Reviewed: 02/21/2025
Document History:

- 02/21/2025 – Annual Review: No criteria changes. Reference updates. Coding Reviewed: Removed ICD-10-CM D05.00-D05.92 and Z17.0.
- 02/23/2024 – Annual Review: No Changes. Coding Reviewed: No Changes.
- 02/24/2023 – Annual Review: No Changes. Coding Review: No changes.
- 02/25/2021 – Annual Review: Update existing criteria for use in HER2-positive breast cancer with NCCN 2A recommendations. Minor wording and formatting updates. Coding Reviewed: No changes.
- 02/19/2021 – New Document: Add new clinical criteria document for Margenza prior authorization. Coding reviewed: Added HCPCS codes J3490, J3590, J9999. All diagnosis pend. Effective 7/1/2021 Added HCPCS J9353. Removed HCPCS J3490, J3590, J9999. Added ICD-10-CM C50.011-C50.929, D05.00-D05.92, C79.81, Z85.3, Z17.0.

References

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3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
4. Margenza (margetuximab-cmkb) intravenous infusion [product information]. Rockville, MD: MacroGenics; December 2020.
5. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 11, 2025
    a. Breast Cancer. V6.2024. Revised November 11, 2024.
6. 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
7. 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. J Clin Oncol. 2022 Nov 4:JCO2102937. doi: 10.1200/JCO.21.02937. Online ahead of print.

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.