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Reviewed: 03/12/25

Revised: 04/15/25

Subject: Margetuximab-cmkb (Margenza™)

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DESCRIPTION:

Margetuximab-cmkb (Margenza™) was approved by the U.S. Food and Drug Administration (FDA) in December 2020 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. Use is indicated in combination with chemotherapy.

Margetuximab-cmkb is a chimeric Fc-engineered IgG1 kappa monoclonal antibody, that binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). Upon binding to HER2-expressing tumor cells, margetuximab-cmkb inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain and mediates antibody-dependent cellular cytotoxicity (ADCC). In vitro, the modified Fc region of margetuximab-cmkb increases binding to activating Fc receptor FCGR3A (CD16A) and decreases binding to inhibitory Fc receptor FCGR2B (CD32B). These changes lead to greater in vitro ADCC and NK cell activation.

The safety and efficacy of margetuximab-cmkb plus chemotherapy were evaluated in a phase 3 randomized open-label trial (SOPHIA) of patients with HER2-positive, unresectable or metastatic breast cancer previously treated with two or more prior anti-HER2 therapies (N=536). Patients were excluded for history of clinically significant cardiac disease, active brain metastases, and life expectancy less than 12 weeks. Patients were randomized to margetuximab-cmkb 15 mg/kg (N=266) plus chemotherapy or trastuzumab 6 mg/kg (N=270) plus chemotherapy, each administered in 3-week cycles. The sequential primary endpoints for the study were progression-free survival (PFS) and overall survival (OS).

All but 1 patient had received prior pertuzumab, and 489 (91.2%) had received prior ado-trastuzumab emtansine. Margetuximab-cmkb improved primary PFS over trastuzumab with 24% relative risk reduction (hazard ratio [HR], 0.76; 95% CI, 0.59-0.98; P = .03; median, 5.8 [95% CI, 5.5-7.0] months vs 4.9 [95% CI, 4.2-5.6] months; October 10, 2018). After the second planned interim analysis of 270 deaths,

median OS was 21.6 months with margetuximab-cmkb compared to 19.8 months with trastuzumab (HR, 0.89; 95% CI, 0.69-1.13; P = .33; September 10, 2019), and investigator-assessed PFS showed 29% relative risk reduction favoring margetuximab-cmkb (HR, 0.71; 95% CI, 0.58-0.86; P < .001; median, 5.7 vs 4.4 months; September 10, 2019). Incidence of infusion-related reactions, mostly in cycle 1, was higher with margetuximab-cmkb (35 [13.3%] vs 9 [3.4%]).

Margetuximab-cmkb is included in NCCN guidelines for treatment of Breast Cancer (version 1.2024).

POSITION STATEMENT:

Initiation of margetuximab-cmkb (Margenza) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when **ALL** associated criteria are met:

1. Breast Cancer
    a. Member is diagnosed with recurrent unresectable (local or regional) or stage IV (M1) breast cancer or inflammatory breast cancer with no response to preoperative systemic therapy
    b. Member has HER2-positive disease defined as **ONE** of the following:
        i. Immunohistochemistry (IHC) is 3+
        ii. Dual-probe ISH assay results:
            1. HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number ≥ 4.0 signals/cell
        iii. Concurrent dual-probe ISH assay and IHC results:
            1. HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number <4.0 signals/cell and concurrent IHC 3+
            2. HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+
            3. HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+
    c. Member has received two or more anti-HER2 treatments (ado-trastuzumab (Kadcyla), fam-trastuzumab deruxtecan-nxki injection (Enhertu), trastuzumab (Herceptin), pertuzumab (Perjeta))
    d. Use will be in combination with chemotherapy
    e. Use will not be in combination with another anti-HER2 regimen
    f. Dose does not exceed 15 mg/kg every 21 days
2. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. Member meets one of the following:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. Dose does not exceed 15 mg/kg every 21 days

Approval duration: 6 months

Continuation of margetuximab-cmkb (Margenza) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for margetuximab-cmkb has been previously approved by Florida Blue or another health plan in the past two years for the treatment of breast cancer or other FDA-approved or NCCN supported diagnosis; **OR** the member currently meets all indication-specific initiation criteria
2. Dose does not exceed 15 mg/kg every 21 days

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Intravenous infusion at 15 mg/kg over 120 minutes for the initial dose, then over a minimum of 30 minutes every 3 weeks for all subsequent doses

Dose Adjustments

Left Ventricular Dysfunction

- Assess left ventricular ejection fraction (LVEF) before starting and regularly during treatment.
- Withhold dosing for at least 4 weeks for any of the following:
  - ≥ 16% absolute decrease in LVEF from pretreatment values
  - LVEF below institutional limits of normal (or 50% if no limits are available) and ≥ 10% absolute decrease in LVEF from pretreatment values.
- Dosing may be resumed if, within 8 weeks, LVEF returns to normal limits and absolute decrease from baseline is ≤ 15%. Permanently discontinue if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions for LVEF decline.

Infusion-Related Reactions

- Decrease the rate of infusion for mild or moderate infusion-related reactions (IRRs).
- Interrupt the infusion for dyspnea or clinically significant hypotension.
- Permanently discontinue dosing in patients with severe or life-threatening IRRs.

Drug Availability

- Injection: 250 mg/10 mL (25 mg/mL) in a single-dose vial

PRECAUTIONS:

Boxed Warning

- Left Ventricular Dysfunction
  - May lead to reductions in left ventricular ejection fraction (LVEF).
  - Evaluate cardiac function prior to and during treatment.
  - Discontinue treatment for a confirmed clinically significant decrease in left ventricular function
- Embryo-Fetal Toxicity
  - Exposure during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception

Contraindications

- None

Precautions/Warnings

- Infusion-Related Reactions (IRRs): Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9353	Injection, margetuximab-cmkb, 5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C50.011 – C50.929	Malignant neoplasm of female and male breast

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Adjuvant Treatment: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will return. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biologic therapy. Adjuvant therapy can be used after or in combination with another form of cancer therapy and is commonly used following removal of a cancerous tumor to further help in treatment.

Metastatic cancer: when cancer spreads from the primary site (place where it started) to other places in the body.

Neo-adjuvant treatment: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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5. NCCN Drugs & Biologics Compendium [Internet]. Fort Washington (PA): National Comprehensive Cancer Network; 2025 [cited 3/2/25]. Available from: http://www.nccn.org/professionals/drug_compendium/content/contents.asp/.
6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 3/2/25]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 3/12/25.

GUIDELINE UPDATE INFORMATION:

03/15/21	New Medical Coverage Guideline.
07/01/21	Revision: Added HCPCS code J9353 and deleted code J9999.
04/15/24	Review and revision to guideline consisting of updating position statement and references.
04/15/25	Review and revision to guideline consisting of updating references.