Clinical Policy Title:	margetuximab-cmkb
Policy Number:	RxA.672
Drug(s) Applied:	Margenza™
Original Policy Date:	03/09/2021
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Margetuximab-cmkb is an Fc-engineered IgG1 kappa monoclonal antibody that targets the HER2 oncoprotein. Margetuximab-cmkb is a HER2/neu receptor antagonist that is approved for adult patients with metastatic HER2-positive breast cancer, in combination with chemotherapy, who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. It is produced from recombinant DNA technology in Chinese hamster ovary culture.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
margetuximab-cmkb (Margenza™)	metastatic HER2-positive breast cancer	Must be given in combination with chemotherapy. The dose is 15 mg/kg, administered as an IV infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The first infusion should be administered over 120 minutes; all subsequent doses can be administered over a minimum of 30 minutes. Margetuximab-cmkb should be administered after chemotherapy completion on days that chemotherapy and margetuximab-cmkb are to be administered. If a dose is missed, administer the dose as soon as possible. Adjust the administration schedule to maintain 3-week intervals between doses.	15 mg/kg

Dosage Forms

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

Clinical Policy

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

I. Initial Approval Criteria

A. Breast Cancer (must meet all)**:**

1. Member has a diagnosis of metastatic HER2-positive breast cancer that has progressed on current or most recent chemotherapy regimen;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Member has tried at least two (2) previous therapies (a and b):
   a. At least one prior therapy with anti-HER2-directed (e.g., ado-trastuzumab emtansine, lapatinib, neratinib, trastuzumab, pertuzumab) therapy;
   b. At least one prior therapy indicated for metastatic disease;
5. c. Member has an ECOG performance score of 0 or 1;
6. d. Must be given in combination with a chemotherapy regimen that is recognized in evidence-based guidelines (e.g., ASCO, NCCN);
7. e. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Breast Cancer (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy (e.g., tumor regression, absence of tumor progression);
3. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
ASCO: American Society of Clinical Oncology
ECOG: Eastern Cooperative Oncology Group
FDA: Food and Drug Administration
HER2: Human Epidermal Growth Factor Receptor 2
IV: Intravenous/intravenously
NCCN: National Comprehensive Cancer Network

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name*	Dosing Regimen	Dose Limit/ Maximum Dose
ado-trastuzumab emtansine (Kadcyla®)	The recommended dose of ado-trastuzumab emtansine is 3.6 mg/kg IV infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.	3.6 mg/kg
fam-trastuzumab deruxtecan-nxki (Enhertu®)	The recommended dose of fam-trastuzumab deruxtecan-nxki is 5.4 mg/kg IV infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.	5.4 mg/kg
lapatinib (Tykerb®)	HER2-positive metastatic breast cancer: 1,250 mg given once daily on days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day on days 1-14 in a repeating 21-day cycle HR-positive, HER2-positive metastatic breast cancer: 1,500 mg given once daily continuously in combination with letrozole.	1,500 mg/day
neratinib (Nerlynx®)	The recommended dose of neratinib is 240 mg given once daily with food on days 1–21 of a 21-day cycle plus capecitabine (750 mg/m^2 given orally twice daily) on days 1–14 of a 21-day cycle until disease progression or unacceptable toxicities.	240 mg/day
pertuzumab (Perjeta®)	The initial dose of pertuzumab is 840 mg as an IV infusion, followed every 3 weeks by a dose of 420 mg as an IV infusion over 30 to 60 minutes until disease progression or unacceptable toxicities.	Initial: 840 mg Subsequent: 420 mg
trastuzumab (Herceptin®)	Administer trastuzumab, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as an IV infusion followed by subsequent once weekly doses of 2 mg/kg as ~~as~~ IV infusions until disease progression or unacceptable toxicities.	Initial: 4 mg/kg Subsequent: 2 mg/kg
tucatinib (Tukysa™)	The recommended dosage of tucatinib is 300 mg orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicities.	600 mg/day

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported

- Boxed Warning(s):
  - Left ventricular cardiac dysfunction. Left ventricular cardiac dysfunction occurred in 1.9% of patients treated with margetuximab-cmkb. Margetuximab-cmkb has not been studied in patients with a pre-treatment LVEF less than 50%, a prior history of myocardial infarction or unstable angina within 6 months or congestive heart failure NYHA class II-IV. Withhold margetuximab-cmkb for 16% or greater absolute decrease in LVEF from pre-treatment values or LVEF value below institutional limits of normal and 10% or greater absolute decrease in LVEF from pre-treatment values. Permanently discontinue margetuximab-cmkb if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions due to LVEF decline.
  - Embryo-Fetal Toxicity. Margetuximab-cmkb can cause fetal harm when administered to pregnant women. In post-marketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death. Verify pregnancy status of females of reproductive age prior to the initiation of margetuximab-cmkb. Advise women and females of reproductive potential that exposure to margetuximab-cmkb during pregnancy or within 4 months prior to conception can result in fetal harm.

APPENDIX D: General Information

- Margetuximab-cmkb binds to the extracellular domain of the HER2 oncoprotein. Upon binding to HER2-expressing tumor cells, margetuximab-cmkb inhibitors tumor cell proliferation, reduces shedding of the HER2 extracellular domain, and mediates antibody-dependent cellular cytotoxicity.
- Infusion-related reactions can occur causing fever, chills, arthralgia, cough, dizziness, fatigue, nausea, vomiting, headache, diaphoresis, tachycardia, hypotension, pruritus, rash, urticaria, and dyspnea. Infusion-related reactions were reported in 13% of patients receiving margetuximab-cmkb plus chemotherapy. Monitor patients for infusion-related reactions during margetuximab-cmkb administration and as clinically indicated after the completion of the infusion.
- Dosage disruption due to adverse reactions occurred in 11% of patients receiving margetuximab-cmkb plus chemotherapy. Permanent discontinuation of margetuximab-cmkb due to adverse reactions occurred in 3% of patients. Adverse reactions that occur 15% or more in patients are listed:
  - Dermatologic: Alopecia (18%)
  - Gastrointestinal disorders: Abdominal pain (17%); constipation (19%); diarrhea (25%); increased serum lipase (30%); nausea (33%); and vomiting (21%)
  - Hematologic: Decreased hemoglobin (52%); increased INR (24%); leukopenia (40%); lymphocytopenia (31%); prolonged partial thromboplastin time (32%)
  - Hepatic: Increased serum alanine aminotransferase (32%), increased alkaline phosphatase (21%); increase aspartate aminotransferase (23%)
  - Nervous system disorders: Fatigue (57%); headache (19%); peripheral neuropathy (16%)
  - Neuromuscular & skeletal: Asthenia (57%)
  - Renal: Increased serum creatinine (68%)
  - Miscellaneous: Pyrexia (19%)
- Patients who receive anthracyclines less than 4 months after stopping margetuximab-cmkb may be at increased risk for cardiac dysfunction. Avoid anthracycline-based therapy for up to 4 months after stopping margetuximab-cmkb. If concomitant use is unavoidable, closely monitor patient's cardiac function.
- Safety and effectiveness of margetuximab-cmkb has not been established in pediatric patients.
- No clinically significant differences in margetuximab-cmkb pharmacokinetics were observed based on race or ethnicity.

- Current National Comprehensive Cancer Network (NCCN) breast cancer guidelines do not include margetuximab-cmkb.

References

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/19/2021	03/09/2021