MEDICAL MUTUAL®

Drug Policy

Policy:	**201429-CC**	**Initial Effective Date: 12/30/2014**
Code(s):	**HCPCS J9354**	**Annual Review Date: 07/19/2018**
SUBJECT:	**Kadcyla® (ado-trastuzumab emtansine for intravenous [IV] injection – Genentech, Inc)**	**Last Revised Date: 07/19/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

Overview

Kadcyla, as a single agent, is indicated for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive, metastatic breast cancer who previously received Herceptin® (trastuzumab for intravenous infusion) and a taxane, separately or in combination.[1] Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy. Kadcyla is a HER2-targeted antibody-drug conjugate (ADC) which contains trastuzumab covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC. Emtansine refers to the MCC-DM1 complex. The antibody trastuzumab is a well characterized recombinant monoclonal antibody product produced by mammalian (Chinese hamster ovary) cells, and the small molecule components (DM1 and MCC) are produced by chemical synthesis.

Kadcyla is available as lyophilized powder in single-use vials containing 100 mg or 160 mg per vial.[1] Kadcyla should be reconstituted to a 20 mg/mL solution, which should be diluted. Dilute reconstituted Kadcyla solution using 250 mL of 0.9% Sodium Chloride Injection (do not use Dextrose 5% solution). The diluted solution is infused intravenously over 90 minutes or 30 minutes for the first infusion or subsequent infusions, respectively.

Policy Statement

This policy involves the use of Kadcyla infusion. Prior authorization is recommended for medical benefit coverage of Kadcyla. Approval is recommended for those who meet the conditions of coverage in the **Criteria**, **Dosing**, **Initial/Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Kadcyla, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kadcyla to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Kadcyla is recommended in those who meet one of the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Breast Cancer.**

Criteria. *The patient must meet the following criteria (a, b, c, AND d):*
a) Kadcyla is prescribed by or in consultation with an oncologist; AND
b) The patient has HER2-positive disease; AND
c) Kadcyla is being used for recurrent or metastatic breast cancer; AND
d) Kadcyla is not being used for adjuvant therapy.

Kadcyla, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received Herceptin and a taxane, separately or in combination.[1] Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy. The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 1.2016) indicate that Kadcyla, as a single agent, is recommended for HER2-positive recurrent or metastatic disease with symptomatic visceral disease or visceral crisis and that is hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory.[2] The *preferred* first-line regimen for HER2-positive *recurrent or metastatic (Stage IV) disease* (either hormone receptor-negative or hormone receptor-positive and refractory to endocrine therapy) is Perjeta® (pertuzumab injection for intravenous use) plus Herceptin plus docetaxel (category 1) or paclitaxel (category 2A). Herceptin plus paclitaxel with or without carboplatin or Herceptin plus either docetaxel, vinorelbine, or capecitabine is also recommended in these patients. The guidelines also note that in the metastatic setting, patients previously treated with chemotherapy plus Herceptin without Perjeta may be considered for one line of therapy including both Herceptin plus Perjeta in combination with or without cytotoxic therapy (such as vinorelbine or a taxane). Agents recommended for Herceptin exposed HER2-positive disease include Tykerb® (lapatinib tablets) plus capecitabine; Herceptin plus capecitabine; Herceptin plus Tykerb (without cytotoxic therapy); or Herceptin with other agents. Of note, Kadcyla is no longer recommended in the guidelines for Herceptin exposed HER2-positive disease.

Data using Kadcyla for adjuvant therapy are not available. In one Phase II randomized study, patients (n = 380) with HER2-positive and hormone receptor-positive early breast cancer received 12 weeks of neoadjuvant therapy with Kadcyla 3.6 mg/kg every 3 weeks with or without endocrine therapy (i.e., tamoxifen in premenopausal women or an aromatase inhibitor in postmenopausal women).[3] In a control arm, patients received Herceptin every 3 weeks plus endocrine therapy. After surgery, completion of 1 year of Herceptin was recommended and standard chemotherapy was used at the investigators' discretion. A pre-planned interim analysis (n = 130) showed a pathological complete response rate of 40.5% (Kadcyla alone), 45.8% (Kadcyla plus endocrine therapy), and 6.7% (Herceptin plus endocrine therapy). The difference between the two Kadcyla arms was not statistically significant. Final results are needed to substantiate these findings.

In the pivotal Phase III study (EMILIA), eligible patients had documented progression of unresectable, locally advanced or metastatic HER2-positive breast cancer previously treated with a taxane and Herceptin.[1,4] Patients were

randomized to receive Tykerb plus capecitabine or Kadcyla. Median progression-free survival was 9.6 months with Kadcyla and 6.4 months with Tykerb plus capecitabine (hazard ratio [HR] 0.65; 95% confidence interval [CI]: 0.55, 0.77; P < 0.0001). Median overall survival was 30.9 months with Kadcyla and 25.1 months with Tykerb plus capecitabine (HR 0.682; 95% CI: 0.548, 0.849; P = 0.0006).

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Kadcyla therapy because these are the only patients studied and for whom benefit has been shown.[1] Breast cancer tumors are classified as HER2-positive if they demonstrate HER2 gene amplification by *in situ* hybridization (ISH) method or are scored as 3+ by an immunohistochemistry (IHC) method.[2,5] Samples scored as 2+ by the IHC method are designated as equivocal (borderline) and should be subjected to reflex testing by an ISH method to assign HER2 status. Similarly, samples with equivocal results by an ISH assay must be confirmed by counting additional cells or repeating the ISH assay. If the results continue to be equivocal, then reflex testing with IHC is recommended to assign HER2 status.

Dosing in Breast Cancer.
Dosing must meet the following(a, b, OR c):
a) 3.6 mg per kg IV infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Do not administer at doses greater than 3.6 mg per kg.
b) 3 mg per kg IV infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
c) 2.4 mg per kg IV infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

The approved dose of Kadcyla is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.[1] The maximum dose is 3.6 mg/kg. The first infusion is given over 90 minutes and subsequent infusions are administered over 30 minutes if prior infusions were well tolerated. The dose of Kadcyla should not be re-escalated after a dose reduction is made. If a planned dose is delayed or missed, it should be administered as soon as possible; do not wait until the next planned cycle. The schedule of administration should be adjusted to maintain a 3-week interval between doses. The infusion rate should be slowed or interrupted if the patient develops an infusion-related reaction. Permanently discontinue Kadcyla for life-threatening infusion-related reactions. Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity, or peripheral neuropathy may require temporary interruption, dose reduction, or discontinuation of Kadcyla. Dosing modifications are determined by the prescribing physician. Dosing modifications recommended in the prescribing information are included in Appendix A.

Initial Approval/Extended Approval.
a) *Initial Approval*. Initial approval is for 6 months.
b) *Extended Approval*. Approve at additional 6-month intervals if the patient does not have disease progression, as determined by the prescribing physician.

Duration of Therapy in Breast Cancer: indefinite if the patient does not have disease progression.

Labs/Diagnostics. Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for Kadcyla therapy. See criteria above.

Either an IHC test or an ISH test has been determined to be an acceptable method for making an initial determination of HER2 tumor status in breast cancer.[2,5]

Other Uses with Supportive Evidence

2. Patient has been Started on Kadcyla.

Criteria. *The patient must meet the following criteria (a AND b):*

a) The patient has HER2-positive,recurrent or metastatic breast cancer; AND

b) The patient meets the conditions for coverage required for **Dosing**, **Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for an approved use in this *Herceptin Utilization Review* policy.

Treatment guidelines for breast cancer indicate that patients with tumors IHC 0 or 1+ for HER2 or ISH not amplified (i.e., HER2-negative) have very low rates of HER2-targeted response, and therapy with Herceptin (a component of the Kadcyla antibody-drug conjugate), is not warranted. Treatment guidelines indicate that HER2-tumor status should be determined for primary, recurrent, and metastatic tumors.2,5 Despite concerns regarding accuracy of HER2 assays in clinical practice, either an IHC test or an ISH test has been determined to be an acceptable method for making an initial determination of HER2 tumor status. IHC testing assesses how much HER2 protein is present on the surface of tumor cells, whereas ISH testing measures how many copies of the HER2 gene are present inside each cancer cell. The NCCN guidelines panel endorses American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) HER2 testing guidelines.

3. Other Cancer Indications. Forward to the Medical Director for review on a case-by-case basis.

Waste Management for All Indications.
Weight-based dosing is used; the dose should be calculated and the number of vials needed assessed.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kadcyla has not been shown to be effective or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions are provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other

practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

Prior approval is required for HCPCS Code J9354.

Sources of Information:

1.Kadcyla® for intravenous injection [prescribing information]. South San Francisco, CA: Genentech, Inc.; May 2015.

2.The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 1.2016). © 2015 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 28, 2016.

3.Harbeck N, Gluz O, Christgen M, et al; West German Study Group ADAPT HER2+/HR+ Investigators. Efficacy of 12-weeks of neoadjuvant TDM1 with or without endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer: WSG-ADAPT HER2+/HR+ phase II trial [abstract 506]. J Clin Oncol. 2015; 33(suppl). Available at: http://meetinglibrary.asco.org/print/1983236. Accessed on April 11, 2016.

4.Verma S, Miles D, Gianni L, et al; for the EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-1791.

5.Wolff AC, Hammond EH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31:3997-4014.

OTHER REFERENCES UTILIZED

•Giordano SH, Temin S, Kirshner JJ, et al; American Society of Clinical Oncology. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32:2078-2099.

•Hoffmann-La Roche/Genentech, Inc. A study of trastuzumab emtansine (T-DM1) plus pertuzumab/pertuzumab placebo versus trastuzumab [Herceptin] plus a taxane in patients with metastatic breast cancer (MARIANNE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 Mar 28]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01120184?term=nct01120184&rank=1 NLM Identifier: NCT01120184.

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•Krop IE, Kim SB, González-Martín A, et al; TH3RESA study collaborators. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:689-699.

•Krop IE, Modi S, LoRusso PM, et al. Phase 1b/2a study of trastuzumab emtansine (T-DM1), paclitaxel, and pertuzumab in HER2-positive metastatic breast cancer. Breast Cancer Res. 2016;18:34.

•Krop IE, Suter TM, Dang CT, et al. Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo)adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer. J Clin Oncol. 2015;33:1136-1142.

•Martin M, Fumoleau P, Dewar JA, et al. Trastuzumab emtansine (T-DM1) plus docetaxel with or without pertuzumab in patients with HER2-positive locally advanced or metastatic breast cancer: Results from a phase Ib/IIa study. Ann Oncol. 2016 Apr 6. [Epub ahead of print]

•Miller KD, Diéras V, Harbeck N, et al. Phase IIa trial of trastuzumab emtansine with pertuzumab for patients with human epidermal growth factor receptor 2-positive, locally advanced, or metastatic breast cancer. J Clin Oncol. 2014;32:1437-1444.

•Patel KC, Hageman K, Cooper MR. Ado-trastuzumab emtansine for the treatment of human epidermal growth factor receptor 2-positive metastatic breast cancer. Am J Health Syst Pharm. 2014;71:537-548

APPENDIX A
Dosing Modifications Recommended in Breast Cancer.[1]

Recommended Dose Reduction Schedule for Adverse Events.

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Dose Modification Guidelines for Increased Serum Transaminases (AST/ALT).

Grade 2 (> 2.5 to ≤ 5 x ULN)	Grade 3 (> 5 to ≤ 20 x ULN)	Grade 4 (> 20 x ULN)
Treat at the same dose level.	Do not administer Kadcyla until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level.	Permanently discontinue Kadcyla.

AST – Aspartate aminotransferase; ALT – Alanine aminotransferase; ULN – Upper limit of normal.

Dose Modification Guidelines for Hyperbilirubinemia.

Grade 2 (> 1.5 to ≤ 3 x ULN)	Grade 3 (> 3 to ≤ 10 x ULN)	Grade 4 (> 10 x ULN)
Do not administer Kadcyla until total bilirubin recovers to Grade ≤ 1, and then treat at same dose level.	Do not administer Kadcyla until total bilirubin recovers to Grade ≤ 1, and then reduce one dose level.	Permanently discontinue Kadcyla.

ULN – Upper limit of normal.

Permanently discontinue Kadcyla in patients with serum transaminases > 3 times upper limit of normal (x ULN) and concomitant total bilirubin > 2 x ULN.

Permanently discontinue Kadcyla in patients with nodular regenerative hyperplasia.

Dose Modifications for Left Ventricular Dysfunction.

Symptomatic CHF	LVEF < 40%	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	LVEF > 45%
Discontinue Kadcyla.	Do not administer Kadcyla. Repeat LVEF assessment	Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If LVEF has	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.	Continue treatment with Kadcyla.

	within 3 weeks. If LVEF < 40% is confirmed, discontinue Kadcyla.	not recovered to within 10% points from baseline, discontinue Kadcyla.		

CHF – Congestive heart failure; LVEF – Left ventricular ejection fraction.

Dose Modifications Guidelines for Thrombocytopenia.

Grade 3 **PLT 25,000/mm^3 to 50,000/mm^3**	**Grade 4** **PLT < 25,000/mm^3**
Do not administer Kadcyla until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at same dose level.	Do not administer Kadcyla until platelet count recovers to ≤ Grade1 (≥ 75,000/mm^3), and then reduce one dose level.

PLT – Platelets

Edits and Denials:

Prior approval: Prior approval is required for **HCPCS Codes J9354**. Requests for prior approval will be authorized by a nurse reviewer if submitted documentation meets criteria outlined within the Corporate Medical Policy.

Requests for prior approval will be forwarded to a qualified physician reviewer if submitted documentation does not meet criteria outlined within Corporate Medical Policy.

TOPPS: Claims received with **HCPCS Code J9354** will edit with **Remark Code M3M or M4M** and will be adjudicated in accordance with the Corporate Medical Policy.

Liability: A participating provider will be required to write off charges denied as not medically necessary.

HCPCS Code(s):	
J9354	Injection, ado-traztuzumab emtansine, 1 mg