Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM116	**Last Approval:**	01/10/2019
Title:	Ado-trastuzumab emtansine (Kadcyla®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Kadcyla (Ado-trastuzumab emtansine): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Medication must be prescribed by or in consultation with an oncologist -HER2-positive disease -Recurrent or metastatic breast cancer -Dosing -Initial/Extended Approval -Duration of therapy -Labs/Diagnostics.

BACKGROUND

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.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***

Medicare Members	***Step-utilization of Part D drugs not required.***

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

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 1.2018) 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 agents for HER2-positive *recurrent or metastatic (Stage IV) disease* (either hormone receptor-negative or hormone receptor-positive and refractory to endocrine therapy) includes Perjeta® (pertuzumab injection for intravenous use) plus Herceptin plus docetaxel (category 1) or paclitaxel (category 2A). Other regimens for HER2-positive recurrent or metastatic disease include Herceptin plus paclitaxel with or without carboplatin; Kadcyla alone; or Herceptin plus one of the following drugs: docetaxel, vinorelbine, or capecitabine. Kadcyla as first-line therapy should only be considered in patients not suitable for the preferred treatment. The preferred agents for *Herceptin-exposed HER2-positive recurrent or metastatic disease* include Tykerb® (lapatinib tablets) plus capecitabine; Herceptin plus capecitabine; Herceptin plus Tykerb (without cytotoxic therapy); or Herceptin with other chemotherapy agents. Of note, Kadcyla is no longer recommended in the guidelines for Herceptin exposed HER2-positive disease.

In one Phase III trial (MARIANNE), 1,095 patients with HER2-positive advanced breast cancer and no prior therapy for advanced disease were randomized to receive Herceptin plus a taxane, Kadcyla plus placebo, or Kadcyla plus Perjeta.[4] The primary end point was PFS. Kadcyla alone and Kadcyla plus Perjeta were non-inferior compared to Herceptin plus a taxane; median PFS was 13.7 months with Herceptin plus a taxane, 14.1 months with Kadcyla alone, and 15.2 months with Kadcyla plus Perjeta. Efficacy of Kadcyla was non-inferior but not superior to Herceptin plus a taxane.

Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for Kadcyla therapy because these were the only patients studied and for whom benefit has been shown.[1]

Dosing in Breast Cancer.

Dosing must meet the following(A, B, OR C):[1]

- **A)** 3.6 mg per kg intravenous 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 intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
- **C)** 2.4 mg per kg intravenous 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.

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.

3. Other Cancer Indications. Forward to the Medical Director for review on a case-by-case basis. Other indications supported in NCCN compendium[6] include HER2 mutation-positive non-small cell lung cancer (category 2A).

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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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

SPECIAL CONSIDERATIONS
None.

LIMITATIONS/EXCLUSIONS
Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References	1. Kadcyla® for intravenous injection [prescribing information]. South San Francisco, CA: Genentech, Inc.; July 2016. 2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 1.2018 – March 20, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 20, 2018. 3. 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.

4. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: Primary results from the phase III MARIANNE study. *J Clin Oncol*. 2017;35(2):141-148.
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.
6. The NCCN Drugs & Biologics Compendium. © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 17, 2018. Search term: ado-trastuzumab emtansine.

OTHER REFERENCES UTILIZED

- Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017 May 16. [Epub ahead of print]
- Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol*. 2017 May 16. [Epub ahead of print]
- 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;27(7):1249-1256.

CFR	
WAC	WAC 284-43-2050

RCW		
Contract Citation	☐ WAH	
	☐ IMC	
	☐ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2105	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM to PM	Cindy Bush
05/04/2018	Transferred to new template	Cindy Bush
05/23/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
01/02/2019	Revisions for ESI annual update	Jennifer Farley, PharmD
01/10/2019	Approval	UM Committee

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 within 3 weeks. If LVEF < 40% is confirmed, discontinue Kadcyla.	Do not administer Kadcyla. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% points from baseline, discontinue Kadcyla.	Continue treatment with Kadcyla. Repeat LVEF assessment within 3 weeks.	Continue treatment with 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 PLT count recovers to ≤ Grade 1 (≥ 75,000/mm^3), and then treat at same dose level.	Do not administer Kadcyla until PLT count recovers to ≤ Grade1 (≥ 75,000/mm^3), and then reduce one dose level.

PLT – Platelet(s)