I. PURPOSE
To define and describe the accepted indications for Kadcyla (ado-trastuzumab emtansine) usage in the treatment of cancer

II. DEFINITIONS

**Kadcyla (ado-trastuzumab emtansine):** is a HER2-targeted antibody-drug conjugate. Trastuzumab, a humanized anti-HER2 IgG1 antibody, is joined by a stable linker to DM1, a small molecule microtubule inhibitor. The stable linker is designed to keep DM1 attached to trastuzumab until taken up by a HER2-positive cell. Upon binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1. Once inside the cell, DM1 binds to tubulin, disrupting the microtubule networks in the cell and resulting in apoptosis. In addition, in vitro studies have shown that similar to trastuzumab, ado-trastuzumab emtansine inhibits HER2 receptor signaling, mediates antibody-dependent cell-mediated cytotoxicity, and inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2.

Kadcyla (ado-trastuzumab emtansine) is FDA approved for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, either separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy.

Kadcyla (ado-trastuzumab emtansine) is available as 100 mg and 160 mg vials for injection.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

**Inclusion Criteria:** Kadcyla (ado-trastuzumab emtansine) may be considered medically necessary when any of the following selection criteria is met:
1. **Breast Cancer**
   a. Kadcyla (ado-trastuzumab emtansine) is being used as a single agent in members with **ALL** of the following conditions:
      i. Tumor over expresses the HER2 protein. A positive HER2 test is defined as IHC 3+ or FISH positive
      ii. Used after first progression in the metastatic setting **OR** for recurrence within six months of completing adjuvant therapy
      iii. The member has prior failure, contraindications, or intolerance to trastuzumab.

**Exclusion Criteria:** Kadcyla (ado-trastuzumab emtansine) is not considered medically necessary when any of the following selection criteria is met:

1. Use in the adjuvant setting.
2. Concurrent use with trastuzumab, lapatinib, pertuzumab, or other chemotherapy.
3. Disease progression while taking Kadcyla (ado-trastuzumab emtansine).
4. Dosing exceeds single dose limit of Kadcyla (ado-trastuzumab emtansine) 3.6 mg/kg.
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

**IV. PROCEDURE**

Requests for Kadcyla (ado-trastuzumab emtansine) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration**
   a. 3.6 mg/kg IV infusion every 3 weeks (21-day cycle); infuse first infusion over 90 minutes. If tolerated, subsequent infusions may be administered over 30 minutes.

2. **Dosage Adjustments**
   a. Renal impairment: dose adjustments cannot be recommended because of limited data.
   b. Hepatic impairment:
      i. AST/ALT > 5 times ULN: Withhold ado-trastuzumab emtansine. Resume treatment at a reduced dose when AST/ALT is less than or equal to 5 times ULN.
         1. First dose reduction: reduce the dose to 3 mg/kg.
         2. Second dose reduction: reduce the dose to 2.4 mg/kg.
ii. Total bilirubin > 1.5 to 3 times ULN: Withhold ado-trastuzumab emtansine. Resume treatment at the same dose level when total bilirubin recovers to less than 1.5 times ULN.

iii. Total bilirubin > 3 times ULN: Withhold ado-trastuzumab emtansine. Resume treatment at a reduced dose when total bilirubin recovers to less than 1.5 times ULN.

1. First dose reduction: reduce the dose to 3 mg/kg.
2. Second dose reduction: reduce the dose to 2.4 mg/kg.

c. Left Ventricular Dysfunction: LVEF is less than 40%, interrupt ado-trastuzumab emtansine therapy and repeat LVEF assessment within 3 weeks. If LVEF is confirmed less than 40%, or if the patient develops symptomatic congestive heart failure, discontinue therapy.

d. Peripheral Neuropathy, grade 3 or 4: interrupt ado-trastuzumab emtansine therapy until recovery to grade 2 or lower.

e. Grade 3 thrombocytopenia (25,000 to less than 50,000/mm(3)): interrupt ado-trastuzumab emtansine therapy until recovery to grade 1 or lower (75,000/mm(3) or greater), and then re-treat with the same dose. If grade 4 thrombocytopenia (less than 25,000/mm(3)) occurs, interrupt therapy until recovery to grade 1 or lower (75,000/mm(3) or greater) and then reduce the dose by 1 level; first dose reduction to 3 mg/kg every 3 weeks or second dose reduction to 2.4 mg/kg every 3 weeks; if further dose reduction is needed, discontinue treatment. Do NOT re-escalate the dose after a reduction is made.

3. Monitoring

a. Assess HER-2 expression status prior to ado-trastuzumab emtansine initiation.

b. Clinical and radiologic evidence of tumor regression is indicative of efficacy.

c. Monitor hepatic function, including serum transaminases and bilirubin, prior to initiation and before each subsequent dose. Hepatotoxicity, ranging from asymptomatic, transient elevation of transaminases to fatal cases, has been reported.

d. Evaluate left ventricular function (LVEF) prior to and at regular intervals (eg every 3 months) during treatment. If LVEF is 45% or less reevaluate in 3 weeks.

e. Verify negative pregnancy status prior to ado-trastuzumab emtansine initiation. Pregnancy should be avoided; trastuzumab is a known teratogen.

f. Extravasation has been reported; monitor infusion site

g. Monitor for signs of infusion reactions during ado-trastuzumab emtansine treatment, especially during the first infusion, and for at least 90 minutes following the first infusion and 30 minutes following subsequent infusions. Infusion reactions, serious (eg, flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia), have been reported with ado-trastuzumab emtansine administration; discontinue therapy for serious infusion reactions

h. Monitor platelet counts prior to initiation, and before each subsequent dose in all patients and during treatment in patients with thrombocytopenia or those on anticoagulant therapy.
i. Monitor for signs of neurotoxicity throughout ado-trastuzumab emtansine treatment. Neuropathy has been reported; therapy interruption may be necessary.

j. Nodular regenerative hyperplasia of the liver has occurred; permanently discontinue if condition occurs

k. Pulmonary toxicity, serious (e.g., dyspnea, interstitial pneumonitis, pulmonary infiltrates, and acute respiratory distress syndrome), some cases fatal, has been reported; discontinue therapy if interstitial lung disease or pneumonitis occur

l. Can cause fetal harm when administered to a pregnant woman.

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

VII. REFERENCES