Kadcyla (ado-trastuzumab)

Background
Kadcyla (ado-trastuzumab) is indicated for HER2-positive breast cancer. Kadcyla is a monoclonal antibody that targets and inhibits HER-2 receptor signaling. Kadcyla inhibits shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2. Kadcyla binds to HER-2 receptors and undergoes internalization, which in turn releases cytotoxic catabolites that disrupt microtubule networks in the cell resulting in cell cycle arrest and apoptotic cell death (1).

Regulatory Status
FDA approved indication:
Kadcyla is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: (1)
- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within 6 months of completing adjuvant therapy.

Kadcyla, as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment (1).
Kadcyla has a boxed warning citing the risk of hepatotoxicity. Serious hepatotoxicity has been reported, including liver failure and death in patients treated with Kadcyla. Serum transaminases and bilirubin levels should be obtained prior to initiation of treatment and prior to each dose (1).

Kadcyla carries a boxed warning citing the risk of cardiac toxicity. Kadcyla administration may lead to reductions in left ventricular ejection fraction (LVEF). Patients should be evaluated for left ventricular ejection fraction prior to and during treatment with Kadcyla (1).

Kadcyla carries a boxed warning citing the risk of fetal harm. Exposure to Kadcyla can result in embryo-fetal death or birth defects. Patients should be advised of these risks and the need for effective contraception during treatment with Kadcyla and for 6 months following the last dose of Kadcyla. Kadcyla is pregnancy category D (1).

Kadcyla may cause pulmonary toxicity and should be discontinued in patients who develop interstitial lung disease (ILD) or pneumonitis. Kadcyla may cause thrombocytopenia and platelet counts should be monitored prior to initiation of therapy and prior to each dose (1).

Treatment with Kadcyla has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR) and/or hypersensitivity; treatment with Kadcyla is not recommended for these patients. Patients should be observed closely for IRR reactions, especially during the first infusion (1).

Safety and effectiveness in pediatric patients have not been established (1).

Related policies
Perjeta, Trastuzumab

Policy
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Kadcyla may be considered medically necessary in patients 18 years of age and older with HER2-positive breast cancer and if the conditions indicated below are met.

Kadcyla is considered investigational in patients that are under 18 years of age and for all other indications.
Prior-Approval Requirements

Age
18 years of age or older

Diagnosis

Patient must have ONE of the following:

1. HER2-positive metastatic breast cancer
   a. Received prior therapy with trastuzumab or trastuzumab with a taxane OR
   b. Developed disease recurrence during or within six months of completing adjuvant therapy

2. HER2-positive early breast cancer
   a. Patient has residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment

AND ALL of the following:
   a. Hepatic function and platelet counts monitored prior to initiation and prior to receiving each dose
   b. Left ventricular ejection fraction (LVEF) monitored prior to initiation and every three months during treatment
   c. Prescriber agrees to advise female patients of reproductive potential to use effective contraception during treatment and for 7 months following the last dose
   d. Prescriber agrees to monitor for pulmonary toxicity

Prior – Approval Renewal Requirements

Age
18 years of age or older

Diagnosis

Patient must have the following:

1. HER2-positive breast cancer

AND ALL of the following:
a. Patient has not been diagnosed with nodular regenerative hyperplasia (NRH)
b. Hepatic function, LVEF and platelet count monitored prior to each dose
c. Prescriber agrees to advise female patients of reproductive potential to use effective contraception during treatment and for 7 months following the last dose
d. Prescriber agrees to monitor for pulmonary toxicity

Policy Guidelines
Pre - PA Allowance
None

Prior - Approval Limits
Duration 12 months

Prior – Approval Renewal Limits
Same as above

Rationale
Summary
Kadcyla is a monoclonal antibody that inhibits the HER2 receptor signaling and mediates antibody-dependent cell-mediated cytotoxicity. This inhibits the shedding of the HER2 extracellular domain in overexpressing HER2 breast cancer cells. Kadcyla carries a boxed warning for an increased risk for liver injury, cardiac toxicity and teratogenicity. Liver function tests should be obtained prior to and during the therapy. Patient should also be monitored for left ventricular ejection fraction prior to initiating Kadcyla, as the drug may cause severe cardiac toxicity. The safety and efficacy of Kadcyla in pediatric patients have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of Kadcyla while maintaining optimal therapeutic outcomes.

References
**5.21.32**

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<th>Prescription Drugs</th>
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<td>Subsection:</td>
<td>Antineoplastic Agents</td>
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### Policy History

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<tr>
<td>March 2013</td>
<td>Addition to PA&lt;br&gt;<strong>Look alike-sound alike warning:</strong> It is important to check the vial labels to ensure that the drug administered is Kadcyla (ado-trastuzumab emtansine) and <strong>NOT</strong> trastuzumab.</td>
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<tr>
<td>June 2013</td>
<td>Clarified language in the Policy and Prior Approval Requirement Section</td>
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<tr>
<td>September 2014</td>
<td>Annual editorial review and reference update&lt;br&gt;Removed weight based dosing, do not substitute with trastuzumab and serum Transaminases and bilirubin limits</td>
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<td>June 2015</td>
<td>Annual editorial review and reference update</td>
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<td>June 2016</td>
<td>Annual editorial review and reference update&lt;br&gt;Policy code changed from 5.04.32 to 5.21.32</td>
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<td>June 2017</td>
<td>Annual editorial review and reference update&lt;br&gt;Addition of age limit to renewal requirements</td>
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<td>June 2018</td>
<td>Annual editorial review and reference update</td>
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<td>May 2019</td>
<td>Addition of indication: HER2-positive early breast cancer. Addition of requirements for monitoring for pulmonary toxicity and embryo-fetal toxicity</td>
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<td>Annual review</td>
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### Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 6, 2019 and is effective on January 1, 2020.