I. PURPOSE
To define and describe the accepted indications for Ixempra (ixabepilone) usage in the treatment of cancer.

II. DEFINITIONS
Ixempra (ixabepilone): is a semisynthetic analog of epothilone B, a microtubule stabilizing agent. Ixabepilone directly binds to beta-tubulin subunits on microtubules and promotes tubulin polymerization and microtubule stabilization via inhibition of depolymerization. Microtubule stabilization leads to microtubule bundles, and the formation of microtubule bundles is plasma ixabepilone concentration-dependent. Alterations in spindle formation cause G2/M phase cell cycle arrest, which causes apoptosis. In addition to direct antitumor activity from cell cycle arrest, ixabepilone has antiangiogenic activity. Normally, microtubules modulate interactions with growth factors. In addition, Ixabepilone appears to have a low susceptibility to various mechanisms involved in the development of tumor resistance. Ixabepilone possesses low susceptibility to multiple tumor resistance mechanisms including efflux transporters such as MRP-1 and P-glycoprotein (P-gp).

Ixempra (ixabepilone) is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Ixabepilone is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

Ixempra (ixabepilone) is available as 15 and 45 mg vials.

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 be supported by, at minimum, two peer reviewed citations. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Ixempra (ixabepilone) may be considered medically necessary when any of the following selection criteria is met:
1. **Breast Cancer**
   
   a. The member has a diagnosis of recurrent or metastatic breast cancer and Ixempra (ixabepilone) is being used for any of the following:
      
      i. In combination with capecitabine for disease resistant to treatment with an anthracycline and a taxane OR whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated OR
      
      ii. In combination with trastuzumab for human epidermal growth factor receptor 2-positive recurrent or metastatic trastuzumab-exposed disease OR
      
      iii. As a single agent in members whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine AND ONE of the following:
          
          1. Hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis
          2. HER2-negative and either hormone receptor-negative, or hormone receptor-positive and endocrine therapy refractory
          3. Progressive with no clinical benefit after three consecutive endocrine therapy regimens or with symptomatic visceral disease.

   **Exclusion Criteria:** Ixempra (ixabepilone) is not considered medically necessary when any of the following selection criteria is met:
   
   1. Ixempra is being used as adjuvant chemotherapy.
   2. Dosing exceeds single dose limit of 40mg/m² of Ixempra.
   3. Contraindicated with capecitabine in patients with AST or ALT greater than 2.5 times the upper limit of normal (ULN) or bilirubin greater than one times ULN due to increased risk of toxicity and neutropenia-related death.
   4. Member has disease progression while taking Ixempra.
   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 Ixempra (ixabepilone) 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. Breast cancer: 40 mg/m² IV over 3 hours, given every 3 weeks. Doses for patients with body surface area greater than 2.2 m² should be calculated based on 2.2 m². Premedicate 1 hr before each infusion with an H1 antagonist (diphenhydramine 50 mg orally or equivalent) and an H2 antagonist (ranitidine 150 to 300 mg orally or equivalent); additionally premedicate with a corticosteroid (dexamethasone 20 mg IV 30 min before infusion or orally 60 min before infusion) in patients with a previous hypersensitivity reaction.
a. Hepatic impairment (bilirubin greater than 1 x ULN or AST/ALT greater than 2.5 x ULN), when used in combination with capecitabine: do not administer.

b. Hepatic impairment (bilirubin greater than 1.5 x ULN and up to 3 x ULN, and AST and ALT of up to 10 x ULN), when used as monotherapy: use starting dose of 20 mg/m²; further dose reductions may be necessary on subsequent courses; may escalate dose up to MAX of 30 mg/m² in subsequent cycles, if tolerated.

c. Concomitant strong CYP3A4 inhibitors and grapefruit juice: avoid if possible; if use is necessary, consider reducing the dose to 20 mg/m²; after discontinuation of a strong CYP3A4 inhibitor, a 1-week washout period is necessary before increasing the dose to the indicated dose. If the strong inhibitor is discontinued, allow a washout period of approximately 1 week before the ixabepilone dose is adjusted upward to 40 mg/m² IV over 3 hours, given every 3 weeks.

d. Febrile neutropenia: delay treatment to allow recovery (including until neutrophil count is 1500/mm³ or more), then reduce dose by 20% when given either as monotherapy or in combination with capecitabine; if toxicity recurs, delay treatment until recovery again, and then decrease the dose by an additional 20%; if concurrent diarrhea or stomatitis occurs in combination therapy, stop capecitabine until the neutrophil count is greater than 1000/mm³ then restart at the same dose.

e. Neutrophil count less than 500/mm³ for 7 or more days: delay treatment until neutrophil count is 1500/mm³ or more, then decrease dose by 20% when given either as monotherapy or in combination with capecitabine; if toxicity recurs, delay treatment until recovery again, then decrease the dose by an additional 20%; if concurrent diarrhea or stomatitis occurs in combination therapy, stop capecitabine until the neutrophil count is greater than 1000/mm³ then restart at the same dose.

f. Platelet count less than 25,000/mm³ or platelet count less than 50,000/mm³ with bleeding: delay treatment until platelet count is 100,000/mm³ or more, then decrease dose by 20% when given either as monotherapy or in combination with capecitabine; if toxicity recurs, delay treatment until recovery again, then decrease dose by an additional 20%; if concurrent diarrhea or stomatitis occurs in combination therapy, stop capecitabine until the platelet count is greater than 50,000/mm³ then restart at the same dose.

g. Neuropathy (grade 2 lasting 7 or more days or grade 3 lasting less than 7 days): delay treatment to allow recovery to grade 1 or less, then decrease dose by 20% when given either as monotherapy or in combination with capecitabine; if toxicity recurs, delay treatment until recovery again, then decrease the dose by an additional 20%.

h. Neuropathy (grade 3 lasting 7 or more days or disabling): discontinue ixabepilone.

i. Arthralgia, myalgia, or fatigue (transient grade 3): delay treatment to allow recovery to grade 1 or less, then restart at the same dose.

j. Hand-foot syndrome (grade 3): delay treatment to allow recovery to grade 1 or less, then restart at the same dose.

k. Grade 3 toxicity besides neuropathy, hand-foot syndrome, or transient arthralgia, myalgia, or fatigue: delay treatment to allow recovery to grade 1 or less, then decrease the dose by 20% when given either as monotherapy or in combination with capecitabine; if toxicity recurs, delay treatment until recovery again, then decrease the dose by an additional 20%.

l. Grade 4 toxicity: discontinue ixabepilone.
3. **Monitoring**
   
a. Radiographic (eg, computed tomography) evidence of breast tumor response.
   
b. Liver function tests; before initiation and periodically.
   
c. Peripheral blood cell count; at baseline and frequently during therapy.

V. **APPROVAL AUTHORITY**

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

VI. **ATTACHMENTS**

VII. **REFERENCES**