Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Ixabepilone (Ixempra®)	MP-RX-FP-46-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Ixabepilone (Ixempra®),* a microtubule inhibitor approved by the Food and Drug Administration (FDA) for the treatment of certain patients with metastatic or locally advanced breast cancer.

Background Information

Ixempra is a microtubule inhibitor, classified as an epothilone. Similar to taxanes, epothilones bind to b-tubulin sites which polymerize and stalize microtubules, thus preventing mitosis and causing apoptosis. While this mechanism is similar to taxanes, epothilones appear to bind to different sites than taxanes and remain active in cases of Taxane resistance.

The FDA approved indications for Ixempra includes 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 or as monotherapy after failure of an anthracycline, a taxane, and capecitabine.

The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Ixempra in the treatment of recurrent or metastatic breast cancer. NCCN recommends Ixempra in combination therapy with trastuzumab in human epidermal growth factor receptor 2 (HER2)+ positive disease that is hormone receptor- negative or hormone receptor-positive with or without endocrine therapy (Perez E, et al 2007).

Ixempra has a black box warning for toxicity in hepatic impairment. Ixempra in combination with capecitabine must not be given to patients with AST or ALT > 2.5 X ULN or bilirubin >1 X ULN due to increased risk of toxicity and neutropenia-related death.

<u>Definitions and Measures</u>

- Anthracycline resistance: Progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting.
- Line of Therapy:
    - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.

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- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

- Locally advanced cancer: Cancer that has spread only to nearby tissues or lymph nodes.
- Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- Microtubule inhibitors (MTI): A class of drugs including taxanes, vinca alkaloids, and epothilones that stabilize or destabilize microtubules, thereby suppressing microtubule dynamics required for proper mitotic function, effectively blocking cell cycle progression and resulting in cell death.
- Taxane resistance: Progression during therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

Approved Indications

Ixempra is indicated by the FDA for treatment:

A. In combination with capecitabine for 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.
B. As a single agent for patients with metastatic or locally advanced breast cancer after failure of an anthracycline, a taxane, and capecitabine.

Other Uses

i. Another NCCN recommendation with a category 2A level of evidence for the use of Ixempra as single agent therapy for recurrent or metastatic breast cancer HER2- negative disease that is hormone receptor-negative or hormone receptor-positive with visceral crisis or refractory to endocrine therapy. This recommendation was based on three phase II studies; however, these studies support the FDA indication and not the specific population of individuals within this 2A recommendation. The recommendation is to continue to wait for appropriate clinical studies in this area.

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9207	Injection, ixabepilone, 1 mg [Ixempra]

ICD-10	Description
C50.011-C50.929	Malignant neoplasm of breast
C56	Malignant neoplasm of ovary
C57.0	Malignant neoplasm of fallopian tube
C48.2	Malignant neoplasm of peritoneum, unspecified
C79.81	Secondary malignant neoplasm of breast
Z85.3	Personal history of malignant neoplasm of breast
Z17.0	Estrogen receptor positive status [ER+]
Z17.1	Estrogen receptor positive status [ER-]

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Ixabepilone (Ixempra®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of breast cancer, metastatic or locally advanced: **AND**

ii. *Any* of the following indications:

A. As monotherapy in individuals treated with two prior lines of therapy (Label, NCCN 2A);

OR

B. In combination with capecitabine in individuals previously treated with two lines of therapy, or whose cancer is taxane resistant and further anthracycline therapy is contraindicated (Label);

OR

C. In combination with trastuzumab (or trastuzumab biosimilars) in individuals with disease resistant to treatment with taxanes (NCCN 2A);

OR

D. As fourth-line therapy and beyond in combination with trastuzumab (or trastuzumab biosimilars) in the treatment of an individual with locally recurrent or metastatic HER2-positive breast cancer with either (NCCN 2A);

1. Hormone receptor-negative disease;

OR

2. Hormone receptor-positive with or without endocrine therapy.

E. As single agent therapy for recurrent unresectable or stage IV HER2-negative disease that is HR-positive with visceral crisis or endocrine therapy refractory used in one of the following lines of therapy (NCCN 2A):

1. As first-line therapy if no germline BRCA 1/2 mutation;

OR

2. As second-line therapy if not a candidate for fam trastuzumab deruxetecan-nxki;

OR

3. As third-line therapy and beyond;

F. As single agent therapy for recurrent unresectable or stage IV triple negative breast cancer (TNBC) used in one of the following lines of therapy (NCCN 2A):

1. First-line therapy if PD-L1 CPS <10 and no germline BRCA 1/2 mutation;

OR

2. Second-line therapy and beyond.

OR

iii. Individual has a diagnosis of Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (NCCN 2B); **AND**

A. Individual has platinum-resistant persistent disease or recurrence; **AND**

B. Has been previously treated with taxane; **AND**

C. Is being used in combination with bevacizumab**.**

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Ixabepilone (Ixempra®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of an unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

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A. A current oncology note documenting the patient's response to treatment showing no progression of disease.

B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. If the baseline neutrophil count is <1500 cells/mm^3 or the platelet count is < 100,000 cells/mm^3;

OR

ii. If Ixempra is used in combination with capecitabine and individual has hepatic impairment defined as AST or ALT > 2.5 x ULN or bilirubin > 1 x ULN;

OR

iii. When the above criteria (Section A; Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

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Drug	Recommended Dosing Schedule[a]
Ixabepilone (Ixempra®)	40 mg/m^2 administered intravenously over 3 hours every 3 weeks

Exceptions

- Dosages for patients whose body surface area (BSA) exceeds 2.2 m2 should be calculated using a baseline of 2.2 m2 as the reference.
- The dose of Ixempra should be modified in patients with hepatic impairment.
  - If AST and ALT ≤10 x ULN and bilirubin ≤1.5x ULN: Ixempra dose should be 32 mg/m^2
  - If AST and ALT ≤10 x ULN and bilirubin >1.5to ≤ 3 x ULN: Ixempra dose should be 20-30 mg/m2 (dose can be increased to 30 mg/m^2 in subsequent cycles if a dose of 20 mg/m^2 is tolerated
  - If AST and ALT >10 x ULN and bilirubin >3 x ULN: Ixempra should be avoided
  - Ixempra is contraindicated when used with concomitant Capecitabine and AST or ALT >2.5 x ULN or bilirubin >1 x ULN.
- The dose of Ixempra should be modified when the patient is using CYP3A4 strong inhibitors or inducers
  - If coadministration of a strong CYP3A4 inhibitor with Ixempra cannot be avoided, the dose of Ixempra should be reduced to 20 mg/m2.
  - Gradually increase the dose of Ixempra from 40 mg/m2 to 60 mg/m2, as tolerated once a patient has been maintained on a strong CYP3A4 inducer.

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 18, 2023.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
5. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 12, 2023.
    a. Breast Cancer. V4.2022. Revised June 21, 2022.
6. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. J Clin Oncol 2007;25:3407-3414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17606974.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Annual Review 10/13/2025	Add clinical criteria for NCCN 2B Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer. Word formatting; minimal changes. Coding reviewed: addition of ICD 10 C56, C57.0 and C48.2.	10/31/2025	11/10/2025
Annual Review 11/12/2024	Updated existing criteria from NCCN category 2A recommendation for use as fourth line therapy and beyond (previously unstated) when used in combination with trastuzumab (or biosimilars) in locally recurrent or metastatic HER2-positive breast cancer. Add NCCN category 2A recommendations for use in recurrent unresectable or stage IV HER2-negative breast cancer that is HR-positive with visceral crisis or endocrine therapy refractive. Add NCCN category 2A recommendation for use in recurrent unresectable or stage IV TNBC. Add contraindications to may not be approved criteria. Update criteria for combination use with capecitabine due to FDA label update. Minor wording and formatting updates. Coding Reviewed: No changes.	2/24/2025	3/6/2025
Select Review 2/15/2024	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception 11/12/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

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