Ixempra® (ixabepilone)
(Intravenous)

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Document Number: MODA-0472

Last Review Date: 06/02/2020
Date of Origin: 07/01/2019
Dates Reviewed: 07/2019, 06/2020

I. Length of Authorization

Coverage will be for six months and is eligible for renewal.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Ixempra 15 mg powder for injection: 2 vials per 21 days
- Ixempra 45 mg powder for injection: 2 vials per 21 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- 90 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is 18 years or older; **AND**

Universal Criteria [1]

- If used in combination with capecitabine, the patient must not have an AST or ALT > 2.5 x ULN or bilirubin > 1 x ULN; **AND**

Breast Cancer [1,2,4,5,6,8,10,12,18,19,21,25]

- Patient has metastatic or recurrent disease ‡ [2]; **AND**
  - Must be used as a single agent for human epidermal growth factor receptor 2 (HER2)-negative disease after prior treatment with an anthracycline; **AND**
    - Patient's disease is hormone receptor negative; **OR**
    - Patient's disease is hormone receptor positive with visceral crisis or is refractory to endocrine therapy; **OR**
  - Must be used in combination with trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive disease; **AND**
    - Patient's disease is hormone receptor negative; **OR**
    - Patient's disease is hormone receptor positive and used with or without endocrine therapy; **OR**

- Patient has locally advanced or metastatic disease † [1]; **AND**
  - Patient has failed on an anthracycline* and a taxane** (or taxane resistant and further anthracycline therapy is contraindicated); **AND**
    - Must be used in combination with capecitabine; **OR**
    - Must be used as a single agent after failure on capecitabine

**Anthracycline resistance: defined as progression of disease while on therapy or within 6-months in the adjuvant setting, or 3-months in the metastatic setting.*

***Taxane resistance: defined as progression of disease while on therapy or within 12-months in the adjuvant setting, or 4-months in the metastatic setting.*

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia recommended indication(s)

IV. Renewal Criteria [1]

Authorizations can be renewed based on the following criteria:

- Patient continues to meet universal or indication specific criteria as in Section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: peripheral neuropathy, myelosuppression (neutropenia, leukopenia, anemia, and thrombocytopenia), hepatic impairment, hypersensitivity reactions, cardiac ischemia, impaired cardiac function, etc.

V. Dosage/Administration

Indication	Dose
Breast Camcer	40 mg/m² administered intravenously (IV) over 3 hours every 21 days. (*Doses for patients with a BSA > 2.2 m² should be calculated based on 2.2 m²*)

VI. Billing Code/Availability Information

HCPCS code:
J9207 – Injection, ixabepilone, 1mg: 1mg = 1 billable unit
NDC:

- Ixempra 15 mg powder for injection: 70020-1910-xx
- Ixempra 45 mg powder for injection: 70020-1911-xx

VII. References

1. Ixempra [package insert]. Princeton, NJ; R-Pharm US LLC; January 2016. Accessed May 2020.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for ixabepilone. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed May 2020.
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer, Version 4.2020. National Comprehensive Cancer Network, 2019. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed May 2020.
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29. CGS, Administrators, LLC. Local Coverage Article: Billing and Coding: Ixabepilone; Ixempra Injection -J9207 (A57257). Centers for Medicare & Medicaid Services, Inc. Updated on 09/18/2019 with effective date 09/26/2019. Accessed April 2020.
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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast

ICD-10	ICD-10 Description
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
Z85.3	Personal history of malignant neoplasm of breast

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): J & M	**NCD/LCD/LCA Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

Jurisdiction(s): 15	**NCD/LCD/LCA Document (s):** A57257
https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?DocID=A57257&bc=gAAAAAAAAAAA&	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; TDP = time to disease progression

Breast Cancer

Metastatic or recurrent breast cancer – HER2 negative							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ixabepilone	2A	Yes (after failure of an anthracycline, a taxane, and capecitabine)	Phase 2, multi-center	N/A	ORR	After 2 or more chemotherapy regimens including an anthracycline, taxane, and capecitabine (HER2-positive patients must have progressed during or after trastuzumab)	• As single agent treatment, ixabepilone resulted in an ORR of 11.5% with a median duration of response of 5.7 months.
Ixabepilone	2A	Yes (after failure of an anthracycline, a taxane, and capecitabine)	Phase 2	N/A	ORR	First-line for metastatic disease (prior anthracycline-based adjuvant treatment)	• Ixabepilone demonstrated an ORR of 41.5% in women with metastatic breast cancer previously treated with an adjuvant anthracycline.

Ixabepilone	2A	Yes (after failure of an anthracycline, a taxane, and capecitabine)	Phase 2	N/A	ORR	After prior anthracycline and taxane	• Ixabepilone resulted an ORR of 12% in patients with taxane resistant metastatic breast cancer.
Nab-paclitaxel + bevacizumab	2A	Yes	Phase 3, randomized	Ixabepilone + bevacizumab vs. paclitaxel + bevacizumab	PFS	First-line	• A shorter median PFS and OS was observed with ixabepilone compared to taxanes. • Ixabepilone may be better tolerated with a lower incidence of hematologic toxicity.
Doxorubicin	2A preferred	Yes	Phase 3	Paclitaxel vs. doxorubicin + paclitaxel (AT)	----------	First-line	• Doxorubicin and paclitaxel have similar activity • Combination of doxorubicin + paclitaxel resulted superior ORR and TTF however, did not improve survival compared to single agent therapy
Docetaxel	2A	Yes	Phase 3, randomized, controlled, multicenter, open-label	Paclitaxel	ORR Toxicity	Second-line therapy for metastatic breast cancer or progression within 12 months of adjuvant or neoadjuvant therapy (prior anthracycline therapy required)	• Docetaxel was superior to paclitaxel in terms of OS and TTP • Hematologic and non-hematologic toxicities occurred more frequently in the docetaxel group
Capecitabine	2A preferred	Yes (after paclitaxel/ anthracycline-	Phase 2, open-label	N/A	ORR	Pretreated with	• Capecitabine demonstrated clinical activity with an ORR of 28% in patients with prior anthracycline and taxane therapy.

		containing regimens or resistant to paclitaxel and not a candidate for anthracycline)				anthracycline and taxane	
Gemcitabine	2A preferred	No	Phase 2	N/A	---------	First-line	• Single-agent gemcitabine is active with an ORR of 37.1% and well tolerated as first-line treatment in patients with metastatic breast cancer
Vinorelbine + gemcitabine	2A	No	Phase 3 (GEICAM), multicenter, open-label, randomized	Vinorelbine	PFS	Subsequent therapy after previous anthracycline and taxane treatment	• Patients with metastatic breast cancer assigned gemcitabine and vinorelbine had better progression-free survival compared with those assigned vinorelbine alone. However, this finding did not translate into a difference in overall survival.
Vinorelbine	2A	No	Prospective, multi-center, randomized trial	Melphalan	-----	Anthracycline-refractory	• This randomized trial demonstrates a survival benefit with vinorelbine in anthracycline-refractory compared to melphalan.
Ixabepilone + capecitabine	None	Yes (after failure of an anthracycline and a taxane)	Phase 3, open-label, multi-center	Capecitabine	PFS	Previous anthracycline and taxane treatment (in adjuvant, neoadjuvant, or metastatic setting)	• Ixabepilone plus capecitabine demonstrates superior efficacy to capecitabine alone in patients with metastatic breast cancer pretreated or resistant to anthracyclines and resistant to taxanes

Gemcitabine + paclitaxel (GT)	2A	No	Phase 3, randomized	Paclitaxel (T)	OS	First-line (after adjuvant anthracycline)	• Gemcitabine added to paclitaxel is effective therapy for women with advanced breast cancer who previously received anthracyclines with a significant improvement in OS and TTP.
Docetaxel + capecitabine (DC)	2A	No	Phase 3, randomized, multi-center	Docetaxel + epirubicin (DE)	TTP	First-line	• The DE and DC regimens have similar efficacy but different toxicity. Either regimen can be used as front-line treatment of ABC.
Epirubicin + cyclophosphamide (EC)	2A	No	Phase 3 (AB01), randomized, multi-center	Epirubicin + paclitaxel (EP)	PFS	First-line	• In terms of progression-free survival and overall survival, there was no evidence of a difference between EP and EC. The data demonstrate no additional advantage to using EP instead of EC as first-line chemotherapy for MBC in taxane-naïve patients.
Metastatic or recurrent breast cancer – HER2 positive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ixabepilone + trastuzumab	2A	No	Phase 2, multi-center	N/A	ORR	No prior chemotherapy or trastuzumab and prior trastuzumab for metastatic disease	• The combination of ixabepilone with trastuzumab for the treatment of metastatic HER2-positive breast cancer demonstrated an ORR of 44% in HER2-positive metastatic breast cancer.
Pertuzumab+ trastuzumab + docetaxel	1	Yes	Phase 3 (CLEOPATRA), randomized, double-blind,	Docetaxel + trastuzumab+ placebo	PFS	First-line in metastatic breast cancer (patients with prior	• Pertuzumab group significantly prolonged PFS and OS

			placebo-controlled Second interim analysis			adjuvant or neoadjuvant therapy, with or without trastuzumab, must have an interval of at least 12 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer)	
Trastuzumab+ vinorelbine	2A	No	Phase 3 (HERNATA), randomized	Trastuzumab+ docetaxel	TTP	First-line	• Neither arm demonstrated significant improvement in survival • However, vinorelbine combination was better tolerated than trastuzumab+ docetaxel
Ado-trastuzumab emtansine (T-DM1)	2A	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic	Phase 3 (MARIANNE), randomized	(Docetaxel or paclitaxel)+ trastuzumab vs T-DM1 + pertuzumab (T-DM1 + P)	PFS Safety	First-line therapy in locally advanced or metastatic breast cancer with ≥ 6-month treatment-free interval	• No significant difference in PFS • T-DM1 is an effective and tolerable alternative first-line treatment for HER2-positive metastatic breast cancer

		disease or developed disease recurrence during or within 6 months of completing adjuvant therapy)				since completion of adjuvant therapy	
Ado-trastuzumab emtansine (T-DM1)	2A	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy)	Phase 3 (EMILIA), randomized, open-label	Lapatinib+ capecitabine	PFS OS Safety	Previous treatment with trastuzumab and a taxane (in any setting) • First-line with progression within 6-months after adjuvant therapy • Second-line therapy or later for locally advanced or metastatic disease	• T-DM1 significantly prolonged PFS and OS with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane
Lapatinib+ capecitabine	2A	Yes	Phase 3, randomized	Capecitabine alone	TTP	Second-line therapy or	• Lapatinib+ capecitabine demonstrated a significant benefit in TTP and a trend

						later after prior trastuzumab (metastatic setting) and prior treatment with an anthracycline and a taxane (metastatic or adjuvant setting)	towards an improvement in OS compared to capecitabine alone
Trastuzumab+ lapatinib	2A	No	Phase III (EGF104900 Study), randomized, open-label	Lapatinib monotherapy	PFS	Second-line therapy or later after one or more prior trastuzumab-containing regimens for metastatic disease	• Modest improvement (3 weeks) in PFS with lapatinib+ trastuzumab versus lapatinib alone • 4.5mon OS advantage with lapatinib+ trastuzumab in patients with pretreated HER2-positive metastatic breast cancer
Eribulin	2A preferred	Yes (After 2 or more chemotherapy regimens for metastatic disease. Prior therapy should have included an	Phase 3, randomized Subgroup analysis	Capecitabine	OS and PFS	First-, second-, or third-line therapy for metastatic disease (in patients with prior anthracycline- and taxane-	• Overall, eribulin was not shown to be superior to capecitabine with regard to OS or PFS • In HER2-negative and triple-negative disease, OS advantage was observed with eribulin over capecitabine

		anthracycline and a taxane in either the adjuvant or metastatic setting.)				based therapy)	
Nab-paclitaxel (no premedication)	2A	No	Phase 3, 1:1, randomized, open-label	Paclitaxel (with premedication)	ORR	All lines of therapy for metastatic disease (59% after at least one prior therapy; 77% with prior exposure to anthracycline)	• Nab-paclitaxel demonstrated greater efficacy in ORR and a favorable safety profile compared with standard paclitaxel • No statistically significant difference was observed in first-line patients however, the difference was statistically significant in patients who received nab-paclitaxel as second-line or greater therapy.
Trastuzumab+ capecitabine	2A	No	Phase 3 (TBP), randomized	Capecitabine	TTP	After prior trastuzumab-based therapy (in adjuvant or metastatic setting)	• Continuing trastuzumab and adding capecitabine beyond trastuzumab progression showed a significant improvement in ORR and TTP compared with capecitabine alone • However, difference in OS was not significant