

Nerlynx[®] (neratinib) (Oral)

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I. Length of Authorization

- Coverage will be provided for six months and may be renewed unless otherwise specified.
 - Extended adjuvant therapy for breast cancer may be renewed one time for a total length of therapy of 1 year.

II. Dosing Limits

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

- Nerlynx 40 mg tablet: 6 tablets per day

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

- 240 mg daily

III. Initial Approval Criteria

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria

- Patient's disease is human epidermal growth factor receptor 2 (HER2)-positive*; **AND**
- Patient will avoid concomitant therapy with all of the following:
 - Coadministration with moderate or strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's Wort, etc.), or if therapy is unavoidable, the patient will be monitored closely for adverse reaction and/or dose modifications will be implemented; **AND**
 - Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, grapefruit juice, etc.); **AND**
 - Coadministration with moderate CYP3A4 and P-gp dual inhibitors (e.g., ketoconazole, itraconazole, verapamil, quinidine, etc.); **AND**

- Coadministration with proton pump inhibitors (e.g., lansoprazole, esomeprazole, omeprazole, etc.), or if acid-reduction therapy is required, use of H₂-receptor antagonists or antacids may be used at staggered administration times; **AND**

Breast Cancer †¹⁻⁵

- Used as a single-agent therapy; **AND**
 - Patient has hormone receptor (HR)-positive disease; **AND**
 - Must be used for extended adjuvant treatment; **AND**
 - Patient completed adjuvant trastuzumab-based therapy within the preceding 1 year; **AND**
 - Patient has 4 or more positive nodes; **AND**
 - Patient has a perceived high risk of recurrence; **OR**
- Used in combination with capecitabine; **AND**
 - Used as third-line therapy and beyond; **AND**
 - Patient has inflammatory disease and experienced no response to pre-operative systemic therapy; **OR**
 - Patient has advanced, recurrent, unresectable, or metastatic disease

Central Nervous System (CNS) Cancers ‡ Φ^{3-4,7-8}

- Used in combination with capecitabine; **AND**
- Patient has brain metastases from HER2-positive breast cancer; **AND**
 - Used as initial treatment in patients with small, asymptomatic brain lesions; **OR**
 - Used for relapsed disease in patients with limited brain metastases and stable systemic disease or reasonable systemic treatment options; **OR**
 - Patient has recurrent limited brain metastases; **OR**
 - Used for recurrent disease in patients with extensive brain metastases and stable systemic disease or reasonable systemic treatment options

***HER2-positive overexpression criteria:^{5,6}**

- Immunohistochemistry (IHC) assay 3+; **OR**
- Dual-probe in situ hybridization (ISH) assay HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number ≥ 4.0 signals/cell; **OR**
- Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
 - HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number < 4.0 signals/cell AND concurrent IHC 3+; **OR**
 - HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**

- o HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+

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

IV. Renewal Criteria ¹

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified 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: severe and/or persistent diarrhea, severe hepatotoxicity, etc.; **AND**
- The total length of therapy has not exceeded 1 year when used as extended adjuvant treatment in breast cancer.

V. Dosage/Administration ^{1,8}

Indication	Dose
Breast Cancer	<p><u>Extended adjuvant treatment in early stage disease***</u></p> <ul style="list-style-type: none"> – Administer 240 mg (six tablets) orally once daily with food, continuously until disease recurrence or for up to one year. <p><u>Advanced or metastatic disease in combination with capecitabine***</u></p> <ul style="list-style-type: none"> – Administer 240 mg (six tablets) orally once daily with food, continuously on Days 1-21 of a 21-day cycle in combination with capecitabine on Days 1-14 of a 21-day cycle until disease progression or unacceptable toxicities. <p>***Dose escalation may be considered instead of starting at the 240 mg daily dose as noted below.</p> <ul style="list-style-type: none"> – Week 1 (days 1-7): 120 mg daily (three tablets) – Week 2 (days 8-14): 160 mg daily (four tablets) – Weeks 3 and onwards: 240 mg daily (six tablets)
CNS metastases in breast cancer	Administer 240 mg (six tablets) orally once daily with food, continuously on Days 1-21 of a 21-day cycle in combination with capecitabine on Days 1-14 of a 21-day cycle until disease progression or unacceptable toxicities.
<p><i>Note: Antidiarrheal prophylaxis (e.g., loperamide) is recommended during the first 2 cycles (56 days) of treatment and as needed thereafter.</i></p>	

VI. Billing Code/Availability Information

HCP/PCS code:

- J8999 – Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

NDC:

- Nerlynx 40 mg tablet: 70437-0240-xx

VII. References

1. Nerlynx [package insert]. Los Angeles, CA; Puma Biotechnology, Inc.; June 2021. Accessed July 2021.
2. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016 Mar;17(3):367-77.
3. Saura C, Oliveira M, Feng YH, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial. *Journal of Clinical Oncology* 37, no. 15_suppl(May 20, 2019)1002-1002.
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for neratinib. National Comprehensive Cancer Network, 2021. 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 June 2021.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. Version 4.2021. National Comprehensive Cancer Network, 2021. 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 Guidelines, go online to NCCN.org. Accessed June 2021.
6. Wolff AC, Hammond EH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J Clin Oncol* 2018;36:2105-2122.
7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for CNS Cancers. Version 1.2021. National Comprehensive Cancer Network, 2021. 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 Guidelines, go online to NCCN.org. Accessed June 2021.

8. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol* 2019;37:1081-1089.

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
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

ICD-10	ICD-10 Description
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
C79.31	Secondary malignant neoplasm of brain
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): N/A

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