# 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 with 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 metastases; **OR**
  - Used for relapsed limited brain metastases with either stable systemic disease or reasonable systemic treatment options; **OR**
  - Used for recurrent limited brain metastases; **OR**
  - Used for recurrent extensive brain metastases with either 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**

| |
|---|
| ○ 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); Φ 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 | Extended adjuvant treatment in early stage disease***<br>– Administer 240 mg (six tablets) orally once daily with food, continuously until disease recurrence or for up to one year.<br>Advanced or metastatic disease in combination with capecitabine***<br>– 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.<br>***Dose escalation may be considered instead of starting at the 240 mg daily dose as noted below.<br>– Week 1 (days 1-7): 120 mg daily (three tablets)<br>– Week 2 (days 8-14): 160 mg daily (four tablets)<br>– 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. |
| *Note: Antidiarrheal prophylaxis (e.g., loperamide) is recommended during the first 2 cycles (56 days) of treatment and as needed thereafter.* | |

## VI. Billing Code/Availability Information

HCPCS 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.; March 2022. Accessed May 2022.
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 Oncology37, 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, 2022. 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 2022.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. Version 3.2022. National Comprehensive Cancer Network, 2022. 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 May 2022.
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 2.2021. 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 May 2022.

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: https://www.cms.gov/medicare-coverage-database/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 |