# PRIOR AUTHORIZATION POLICY

**POLICY:** Oncology – Nerlynx Prior Authorization Policy
- Nerlynx® (neratinib tablets – Puma)

**REVIEW DATE:** 06/18/2025

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***INSTRUCTIONS FOR USE***

*THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.*

## CIGNA NATIONAL FORMULARY COVERAGE:

## OVERVIEW

Nerlynx, a kinase inhibitor, is indicated in adults for the following uses:[1]
- Early-stage human epidermal growth factor receptor 2 (HER2)-positive **breast cancer**, as a single agent for extended adjuvant therapy to follow adjuvant trastuzumab-based therapy.
- Advanced or metastatic HER2-positive **breast cancer**, in combination with capecitabine, for patients who have received two or more prior anti-HER2-based regimens in the metastatic setting.

## Guidelines

Nerlynx is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):
- **Breast Cancer:** NCCN guidelines (version 4.2025 – April 17, 2025) note that Nerlynx can be considered as extended adjuvant therapy following adjuvant trastuzumab-containing therapy in patients with hormone receptor

(HR)-positive, HER2-positive disease with a perceived high risk of recurrence and node positive (category 2A).[2] The benefits or toxicities associated with extended Nerlynx in patients who have received Perjeta® (pertuzumab intravenous infusion) or Kadcyla® (ado-trastuzumab emtansine intravenous infusion) are unknown. For the treatment of recurrent unresectable (local or regional) or Stage IV or metastatic HER2-positive disease, Nerlynx + capecitabine is recommended for fourth-line and beyond setting (category 2A). Nerlynx + trastuzumab or fulvestrant (category 2A) or Nerlynx ± fulvestrant (category 2B) is recommended as "useful in certain circumstances" for patients with HER2-activating mutations in the following situations: patients with HER2-negative disease who have HR-positive disease and have already received a cyclin dependent kinase (CDK) 4/6 inhibitor therapy or patients with triple negative disease. HER2-activating mutations occur on the HER2 gene. HER2-activating mutations are clinically distinct from the classification of HER2-positive or HER2-negative disease. Examples of HER2-activating mutations include: L755S, D769H/Y, V777L, or exon 20 insertion.[3]

- **Central Nervous System Cancers**: NCCN guidelines (version 1.2025 – June 3, 2025) list Nerlynx + either capecitabine (category 2A), Kadcyla (category 2A), or paclitaxel (category 2B) for brain metastases for patients with HER2-positive breast cancer.[4]
- **Cervical Cancer**: NCCN guidelines (version 4.2025 – March 24, 2025) recommend Nerlynx as second-line or subsequent therapy for recurrent or metastatic disease as a single-agent for HER2-mutant tumors as "useful in certain circumstances" (category 2A).[5]

## POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nerlynx. All approvals are provided for the duration noted below. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men/males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. Female/women are defined as individuals with the biological traits of a woman, regardless of the individual's gender identity or gender expression.

- **Nerlynx® (neratinib tablets - Puma)**

**is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):**

### FDA-Approved Indications

1. **Breast Cancer – Adjuvant Therapy.** Approve for 1 year (total) if the patient meets ALL of the following (A, B, C, and D):
   **A)** Patient is ≥ 18 years of age; AND

**B)** Patient will not be using this medication in combination with human epidermal growth factor 2 (HER2) antagonists; AND
Note: Examples of HER2 antagonists are trastuzumab and Perjeta (pertuzumab intravenous infusion).
**C)** Patient has HER2-positive breast cancer; AND
**D)** Patient meets ONE of the following (i or ii):
**i.** The medication is requested for extended adjuvant therapy after the patient has completed 1 year of adjuvant therapy with an intravenous trastuzumab product; OR
**ii.** According to the prescriber, patient has tried adjuvant therapy with an intravenous trastuzumab product and could not tolerate 1 year of therapy.

**2. Breast Cancer – Recurrent or Metastatic HER2-Positive Disease.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
**A)** Patient is ≥ 18 years of age; AND
**B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer; AND
**C)** Patient meets ONE of the following (i or ii):
**i.** Patient meets BOTH of the following (a and b):
**a)** The medication is used in combination with capecitabine; AND
**b)** Patient has tried at least two prior anti-HER2 based regimens; OR
Note: Examples include Perjeta (pertuzumab intravenous infusion) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Enhertu (fam-trastuzumab deruxtecan-nxki intravenous infusion), Kadcyla (ado-trastuzumab emtansine intravenous infusion), Tukysa (tucatinib tablets) + trastuzumab + capecitabine, trastuzumab + capecitabine, lapatinib + capecitabine, trastuzumab + lapatinib.
**ii.** Patient meets BOTH of the following (a and b):
**a)** The medication is used in combination with one of the following: capecitabine, paclitaxel, or Kadcyla (ado-trastuzumab emtansine intravenous infusion); AND
**b)** Patient has brain metastases.

**Other Uses With Supportive Evidence**

**3. Breast Cancer – Recurrent or Metastatic HER2-Negative Disease.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
**A)** Patient is ≥ 18 years of age; AND
**B)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
**C)** The cancer has a HER2-activating mutation; AND
Note: HER2-activating mutations are clinically distinct from the classification of HER2-positive or HER2-negative disease. Examples of HER2-activating mutations include: L755S, D769H/Y, V777L, or exon 20 insertion.
**D)** Patient meets ONE of the following (i or ii):
**i.** Patient is a postmenopausal female* or a male*; OR

**ii.** Patient is a pre/perimenopausal female* and meets ONE of the following (a or b):
**a)** Patient is receiving ovarian suppression/ovarian ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), or Zoladex (goserelin acetate subcutaneous implant).
**b)** Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND

**E)** Patient meets ONE of the following (i or ii):
**i.** Patient meets BOTH of the following (a and b):
**a)** Patient has hormone receptor (HR)-positive (i.e., estrogen receptor [ER] or progesterone receptor [PR] positive) disease; AND
**b)** Patient has tried at least one CDK4/6 inhibitor therapy; OR
Note: Examples of CDK4/6 inhibitors are Kisqali (ribociclib tablets), Ibrance (palbociclib capsules and tablets), or Verzenio (abemaciclib tablets).
**ii.** Patient has (HR)-negative (i.e., estrogen receptor [ER] or progesterone receptor [PR] negative) disease.

* Refer to the Policy Statement.

**4. Cervical Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
**A)** Patient is ≥ 18 years of age; AND
**B)** Patient has human epidermal growth factor receptor 2 (HER2)-mutant disease; AND
**C)** Patient has recurrent or metastatic disease; AND
**D)** Patient has tried at least one systemic regimen
Note: Examples of a systemic regimen include one or more of the following medications: Keytruda (pembrolizumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), cisplatin, paclitaxel, bevacizumab, topotecan, carboplatin

## CONDITIONS NOT COVERED

- **Nerlynx® (neratinib tablets - Puma)**

**is(are) considered not medically necessary for ANY other use(s); criteria will be updated as new published data are available.**

## REFERENCES


1. Nerlynx® tablets [prescribing information]. Los Angeles, CA: Puma; March 2022.
2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2025 – April 17, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 10, 2025.
3. Bon G, Sofia Di Lisa F, Filomeno L, et al. HER2 mutation as an emerging target in advanced breast cancer. *Cancer Sci*. 2024; 115(7):2147-2158.

4. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2025 – June 3, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 10, 2025.
5. The NCCN Cervical Cancers Clinical Practice Guidelines in Oncology (version 4.2025 – March 24, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 10, 2025.

## HISTORY

| Type of Revision | Summary of Changes | Review Date |
|---|---|---|
| Annual Revision | No criteria changes. | 10/18/2023 |
| Annual Revision | No criteria changes. | 06/26/2024 |
| Annual Revision | **Breast Cancer – Recurrent or Metastatic HER2-Positive Disease:** Previously this condition of approval was worded as Breast Cancer – Recurrent or Metastatic Disease. The following option for approval was added, "the medication is used in combination with one of the following: capecitabine, paclitaxel, or Kadcyla (ado-trastuzumab emtansine intravenous infusion) and patient has brain metastases."<br>**Breast Cancer – Recurrent or Metastatic HER2-Negative Disease:** This condition of approval and criteria were added to Other Uses with Supportive Evidence.<br>**Cervical Cancer:** This condition of approval and criteria were added to Other Uses with Supportive Evidence. | 06/18/2025 |