Clinical Policy: Neratinib (Nerlynx)

Reference Number: CP.PHAR.365
Effective Date: 12.01.17
Last Review Date: 11.26
Line of Business: Commercial, HIM/ICHRA, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Neratinib (Nerlynx®) is a kinase inhibitor that irreversibly binds to epidermal growth factor receptor, human epidermal growth factor receptor 2 (HER2), and HER4.

FDA Approved Indication(s)

Nerlynx is indicated:

- As a single agent, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
- In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Nerlynx is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Breast Cancer (must meet all)**:**

1. Diagnosis of breast cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. If disease is HER2-positive: Member meets one of the following (a, b, or c):
   a. Both (i and ii):
      i. Documentation of previous adjuvant treatment with trastuzumab (*see Appendix B);*
      ii. Disease is early stage (stage 1-3) or hormone-receptor positive;
   b. Prescribed in combination with capecitabine for recurrent, advanced, or metastatic disease, and member has received two or more prior anti-HER2 based regimens used in the metastatic setting;
   c. Prescribed in combination with Kadcyla®, capecitabine, or paclitaxel for central nervous system brain metastases;
5. If disease is HER2-negative (including triple negative disease) with *HER2* (*ERBB2*) activating mutations: Both of the following (a and b):
   a. Disease is stage IV;

b. One of the following (i or ii):
   i. Prescribed as a single agent;
   ii. Prescribed in combination with fulvestrant;

6. For brand Nerlynx requests, member must use generic neratinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 240 mg (6 tablets) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Cervical Cancer (off-label) (must meet all)**:**

1. Diagnosis of cervical cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease has HER2-mutant tumors;
5. Prescribed as a single agent;
6. Nerlynx is used as subsequent therapy *(see Appendix B for examples*);
7. For brand Nerlynx requests, member must use generic neratinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
8. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 12 months or duration of request, whichever is less

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (member meets all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Nerlynx for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For brand Nerlynx requests, member must use generic neratinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 240 mg (6 tablets) per day;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (member meets 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
HER: human epidermal growth factor receptor
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Breast Cancer		
Herceptin® (trastuzumab) Ogivri™ (trastuzumab-dkst) Ontruzant® (Trastuzumab-dttb) Herzuma® (Trastuzumab-pkrb) Trazimera™ (Trastuzumab-qyyp) Kanjinti™ (Trastuzumab-anns)	Administer according to one of the following doses and schedules for a total of 52 weeks: ***Herceptin, Ogivri, Herzuma, Ontruzant, Trazimera, Kanjinti:*** During and following paclitaxel, docetaxel, or docetaxel/carboplatin: • Initial dose of 4 mg/kg as an IV infusion over 90 minutes then at 2 mg/kg as an IV infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin). • One week following the last weekly dose of the trastuzumab product, administer trastuzumab product at 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks. ***Herceptin, Ogivri, Ontruzant, Trazimera, Kanjinti:*** As a single agent within 3 weeks following completion of multi-modality, anthracycline based chemotherapy regimens: • Initial dose: 8 mg/kg as an IV infusion over 90 minutes. • Subsequent doses: 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks	8 mg/kg

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Herceptin Hylecta™ (Trastuzumab-hyaluronidase-oysk)	***Herceptin Hylecta (subcutaneous product):*** As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; as part of a treatment regimen with docetaxel and carboplatin; or as a single agent following multi-modality anthracycline based therapy: 600 mg trastuzumab and 10,000 units hyaluronidase administered subcutaneously over approximately 2-5 minutes once every 3 weeks for 52 weeks	600 mg/10,000 units every 3 weeks
Perjeta® (pertuzumab)	Initial 840 mg IV followed by a maintenance dose of 420 mg IV every 3 weeks for a total of 52 weeks in combination with trastuzumab and either docetaxel or paclitaxel	Maintenance: 420 mg every 3 weeks
Kadcyla® (ado-trastuzumab emtansine)	3.6 mg/kg IV every 3 weeks	3.6 mg/kg every 3 weeks
Enhertu® (fam-trastuzumab deruxtecan-nxki)	5.4 mg/kg once every 3 weeks	5.4 mg/kg every 3 weeks
Cervical Cancer		
Cisplatin/paclitaxel/bevacizumab	Various	Various
Carboplatin/paclitaxel/bevacizumab	Various	Various
Atezolizumab + cisplatin/paclitaxel + bevacizumab	Various	Various
Atezolizumab + carboplatin/paclitaxel + bevacizumab	Various	Various

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- Nerlynx is FDA-approved for a one year total duration of therapy as it was only administered for one year in the pivotal ExteNET trial; however, the NCCN does not recommend any specific length of treatment.

V. Dosage and Administration

Indication	Dosing Regimen*	Maximum Dose
Breast cancer extended adjuvant treatment	240 mg PO QD	240 mg/day
Breast cancer advanced, recurrent, or metastatic disease	240 mg PO QD on days 1-21 plus capecitabine 750 mg/m^2 PO BID on days 1-14 of a 21-day cycle	240 mg/day

**A two-week dose escalation may be considered instead of starting at the 240 mg daily dose for patients with early-stage breast cancer and metastatic breast cancer: week 1 (days 1-7): 120 mg PO QD; week 2 (days 8-14): 160 mg PO QD.*

VI. Product Availability

Tablet: 40 mg

VII. References

1. Nerlynx Prescribing Information. Los Angeles, CA: Puma Biotechnology, Inc.; December 2025. Available at: https://www.nerlynxhcp.com/pdf/full-prescribing-information.pdf/. Accessed July 10, 2026.
2. National Comprehensive Cancer Network. Breast Cancer Version 6.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 11, 2026.
3. National Comprehensive Cancer Network. Central Nervous System Cancers Version 2.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed August 11, 2026.
4. National Comprehensive Cancer Network. Cervical Cancer Version 2.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed August 11, 2026.
5. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 10, 2026.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2022 annual review: no significant changes; revised generic redirection language to "must use" per updated template; consolidated initial approval duration for Legacy WCG to align with standard Medicaid approach; references reviewed and updated. Template changes applied to other diagnoses/indications.	07.29.22	11.22
4Q 2023 annual review: no significant changes; updated Appendix B to clarify total duration of 52 weeks for Herceptin Hylecta and Perjeta dosing; references reviewed and updated.	07.03.23	11.23
4Q 2024 annual review: for initial criteria, added "paclitaxel" as an option to criterion "prescribed in combination with capecitabine **or paclitaxel** for central nervous system brain metastases" as supported by NCCN compendium and guidelines; references reviewed and updated.	07.12.24	11.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2025 annual review: for breast cancer, added prescribed in combination with Kadcyla for central nervous system brain metastases per NCCN; extended approval duration from 6 months to 12 months for HIM and Medicaid; added criteria for cervical cancer as off-label indication is supported by NCCN compendium and guidelines; references reviewed and updated.	07.10.25	11.25
4Q 2026 annual review: for breast cancer, added off-label criteria for HER2-negative disease per NCCN; added ICHRA line of business; references reviewed and updated.	07.10.26	11.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to

recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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