

**PRIOR AUTHORIZATION POLICY****POLICY:** Oncology – Nerlynx™ (neratinib tablets – Puma Biotechnology)**TAC APPROVAL DATE:** 08/23/2017**LAY CRITERIA EFFECTIVE DATE:** 09/21/2017

OVERVIEW

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2) overexpressed/amplified (i.e., HER2 positive [HER2+]) breast cancer, to follow adjuvant Herceptin® (trastuzumab intravenous infusion) based therapy.¹ Nerlynx is a kinase inhibitor that irreversibly binds to epidermal growth factor receptors (EGFR), HER2, and HER4. *In vitro* studies showed Nerlynx has antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines.

Disease Overview

Based on molecular profiling, breast cancer is classified as hormone receptor positive (HR+) [estrogen receptor positive {ER+} and/or progesterone receptor positive {PgR+}], HER2+, or triple negative (ER-negative, PgR-negative, and HER2-negative).²⁻³ Most breast cancers in women (74%) are HR+, HER2-negative; these cancers tend to be slow-growing and less aggressive than other subtypes.³ HR+, HER2-negative tumors are associated with the most favorable prognosis compared with other subtypes, particularly in the short-term, in part because expression of hormone receptors is predictive of a favorable response to hormonal therapy. In men, about 85% of breast cancers are ER+ and 70% are PgR+.⁴ Up to 20% of patients with breast cancer have HER2+ tumors which are associated with a worse prognosis.^{3,5} About 10% of breast cancers are HR+ and HER2+, and tend to be higher grade and more aggressive than HR+ cancers.³ About 4% of breast cancers are HER2+ and do not express hormone receptors. These cancers tend to be more aggressive than other breast cancers and have a poorer short-term prognosis compared with ER+ breast cancers. However, use of targeted therapies for HER2+ cancers (i.e., Herceptin, Perjeta® [pertuzumab intravenous infusion]) has improved the prognosis of early-stage disease.

Clinical Efficacy

The efficacy of Nerlynx was established in one Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal study (ExteNET, Extended Adjuvant Treatment of Breast Cancer with Neratinib) in women with early stage HER2+ breast cancer (n = 2,840).^{1,5} Patients had completed adjuvant treatment with Herceptin and were without evidence of recurrence. Invasive disease-free survival (iDFS) within 2 years and 28 days was 94.2% (95% confidence interval [CI]: 92.6%, 95.4%) on Nerlynx vs. 91.9% (95% CI: 90.2%, 93.2%) on placebo (stratified hazard ratio 0.66; 95% CI: 0.49, 0.90; P =0.008). Overall survival data are not mature. In a prespecified exploratory subgroup analysis of iDFS, Nerlynx was more beneficial in patients with HR+ breast cancer (unstratified hazard ratio 0.49; 95% CI: 0.31, 0.75) than to patients with HR negative disease (unstratified hazard ratio 0.93; 95% CI: 0.60, 1.43).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 2.2017) have not been updated to include Nerlynx.⁶ These guidelines indicate that for *preoperative/adjuvant treatment* of HER2+ invasive breast cancer (all regimens category 2A), the preferred Herceptin-containing regimens include: doxorubicin/cyclophosphamide (AC) regimen followed by paclitaxel plus concurrent Herceptin

with or without Perjeta; or docetaxel/carboplatin/Herceptin (TCH) regimen with or without Perjeta. Other Herceptin-containing preoperative/adjuvant regimens include: AC followed by docetaxel plus Herceptin with or without Perjeta; docetaxel/cyclophosphamide/Herceptin; 5-fluorouracil/epirubicin/cyclophosphamide (FEC) followed by docetaxel (or paclitaxel) with Herceptin and Perjeta; paclitaxel/Herceptin; or Herceptin and Perjeta with docetaxel (or paclitaxel) followed by FEC. Patients with HER2+ tumors should be treated with preoperative systemic therapy including Herceptin for at least 9 weeks of preoperative therapy. A Perjeta-containing regimen may be given preoperatively in certain patients with HER2+ early-stage breast cancer.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nerlynx. Coverage cumulative with Nerlynx is recommended for up to 1 year of a patient's lifetime. All approvals are provided for 1 year in duration unless otherwise noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nerlynx is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Breast Cancer in Women*:** Approve for up to 1 year if the patient meets the following criteria (A, B, and C):
 - A) Patient has early-stage disease; AND
 - B) Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer; AND
 - C) The patient meets ONE of the following criteria (i or ii):
 - i. Patient has completed 1 year of adjuvant therapy with Herceptin (trastuzumab intravenous injection); OR
 - ii. The patient has tried adjuvant therapy with Herceptin (trastuzumab intravenous injection) and could not tolerate 1 year of therapy, according to the prescribing physician.

* Refer to the Policy Statement.

Other Uses With Supportive Evidence

2. **Breast Cancer in Men*:** Approve for up to 1 year if the patient meets the following criteria (A, B, and C):
 - A) Patient has early-stage disease; AND
 - B) Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer; AND
 - C) The patient meets ONE of the following criteria (i or ii):
 - i. Patient has completed 1 year of adjuvant therapy with Herceptin (trastuzumab intravenous injection); OR

- ii. The patient has tried adjuvant therapy with Herceptin (trastuzumab intravenous injection) and could not tolerate 1 year of therapy, according to the prescribing physician.

* Refer to the Policy Statement.

The NCCN guidelines on breast cancer (version 2.2017) state that men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.⁶ Information is not available using Nerlynx in men with breast cancer.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nerlynx has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use of Nerlynx with Other Medications for Adjuvant or Neoadjuvant Treatment of HER2-Positive Breast Cancer:** Nerlynx is not indicated in combination with other medications for adjuvant or neoadjuvant (preoperative) treatment HER2 positive breast cancer (e.g., Herceptin, Perjeta). Studies are not available for this use. Patients with HR+ early breast can receive concurrent adjuvant estrogen therapy.⁵
2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nerlynx™ tablets [prescribing information]. Los Angeles, CA: Puma Biotechnology, Inc.; July 2017.
2. National Cancer Institute: PDQ® Breast cancer treatment. National Cancer Institute. Date last modified July 13, 2017. Available at: <https://www.cancer.gov/types/breast/hp/breast-treatment-pdq>. Accessed on August 16, 2017.
3. American Cancer Society. *Breast Cancer Facts & Figures 2015-2016*. Atlanta: American Cancer Society, Inc. 2015. Available at: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2015-2016.pdf>. Accessed on August 16, 2017.
4. National Cancer Institute: PDQ® Male breast cancer treatment. National Cancer Institute. Date last modified May 25, 2017. Available at: <https://www.cancer.gov/types/breast/hp/male-breast-treatment-pdq#section/all>. Accessed on August 16, 2017.
5. Chan A, Delaloge S, Holmes FA, et al; ExteNET Study Group. 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;17:367-377.
6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 2.2017 – April 6, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on August 21, 2017.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
New policy	New policy	08/23/2017	09/21/2017

TAC – Therapeutic Assessment Committee. * For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.

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