neratinib (Nerlynx®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO077

Description

Neratinib (Nerlynx) is an orally administered Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 and 4 (HER2, HER4) irreversible inhibitor.

Length of Authorization

- Initial:
  - i. Early stage breast cancer: 12 months
  - ii. Metastatic breast cancer: Six months
- Renewal:
  - i. Early stage breast cancer: Cannot be renewed
  - ii. Metastatic breast cancer: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
neratinib (Nerlynx)	40 mg tablets	Breast cancer, early stage, HER2-positive, following trastuzumab	180 tablets/30 days
		Breast cancer, advanced or metastatic HER2-positive	

Initial Evaluation

I. Neratinib (Nerlynx) may be considered medically necessary when the following criteria are met:
   A. Member is a female 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Neratinib (Nerlynx) will **not** be used in combination with another oncology therapy unless outlined below (e.g. in combination with capecitabine in metastatic disease); **AND**
   D. The member has **not** previously progressed on, or after, treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], tucatinib [Tukysa]); **AND**
   E. A diagnosis of one of the following:
      1. **Early stage (I-III) breast cancer**; **AND**
         i. Documentation is provided showing the disease is HER2-positive AND hormone receptor (HR)-positive; **AND**
         ii. The member has received adjuvant trastuzumab-based therapy (e.g., Herceptin, Trazimera, Kanjinti, etc.) within the past 12 months; **OR**
      2. **Advanced or metastatic breast cancer; AND**
         i. Documentation is provided showing the disease is HER2-positive; **AND**

ii. Member has received ≥2 prior anti-HER2-based regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting; **AND**
iii. Will be used in combination with capecitabine

II. Neratinib (Nerlynx) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Early stage breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
   B. Early stage breast cancer that is not HR-positive
   C. Early stage breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)

III. Neratinib (Nerlynx) is considered investigational when used for all other conditions, including but not limited to:
   A. Triple negative breast cancer
   B. Breast cancer that is HER-2 negative
   C. Non-small cell lung cancer
   D. Colorectal cancer
   E. Head and neck cancer
   F. Ovarian, endometrial, uterine cancer
   G. Bladder or rectal cancer
   H. Early stage breast cancer for greater than one year
   I. Solid tumors, other than breast cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. A diagnosis of **advanced or metastatic breast cancer; AND**
   - Will be used in combination with capecitabine; **AND**
   - Will not be used with any other oncology therapy outside of capecitabine; **AND**
   - Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Neratinib (Nerlynx) was evaluated for safety and efficacy in the ExteNET trial; a randomized, double-blind, placebo-controlled trial in women who had been previously treated with trastuzumab therapy and had HER2-positive breast cancer.

II. Subjects included had early stage (I-III) disease and had completed trastuzumab within the past two years; however, the majority of subjects had received trastuzumab within the past year (81%). Notably, results were statistically significant in those that received trastuzumab within the past year and were not for those that had received treatment 1-2 years prior. The primary outcome was invasive disease-free survival (iDFS) defined as time between date of randomization to first occurrence of invasive recurrence. Results for the iDFS at 24 months was 94.2% for neratinib (Nerlynx) compared to 91.9% for placebo (HR 0.66 [0.49-0.90], p=0.008). Subgroup analyses showed a statistically significant result for those with HR-positive disease but did not for HR-negative disease. Additionally, results favored neratinib (Nerlynx) in those that used therapy after trastuzumab; however, were not significant for those concurrently receiving trastuzumab.

III. Neratinib (Nerlynx) has only been evaluated for safety and efficacy for up to one year of therapy in early stage disease; matching the prescribing information, which notes continuous dosing for one year in this setting.

IV. Neratinib (Nerlynx) was evaluated for safety and efficacy in the advanced or metastatic population in the NALA trial; a randomized, open label, trial evaluating neratinib (Nerlynx) plus capecitabine compared to lapatinib (Tykerb). Patients included in the trial had metastatic HER2-postive breast cancer and had received 2 or more prior anti-HER2 regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting. Median progression free survival (PFS) was 5.6 months with neratinib (Nerlynx) plus capecitabine and 5.5 months with lapatinib plus capecitabine (HR, 0.76; 95% [CI], 0.63 to 0.93; P=0.0059). Overall survival was 21.0 months with the neratinib (Nerlynx) arm and 18.7 months with the lapatinib arm; however, the between group difference was not statistically significant (HR, 0.88; 95% CI, 0.72 to 1.07; P=0.2086).

V. Patients in the NALA trial were excluded if they were previously treated with capecitabine, neratinib, lapatinib, or any other HER2 directed tyrosine kinase inhibitor. At this time, there is a lack of scientific evaluation for safety and efficacy of neratinib (Nerlynx) following progression on, or after, another tyrosine kinase inhibitor.

VI. In the NALA trial, 59% of patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-). Thus, coverage of neratinib (Nerlynx) is available regardless of hormone receptor status.

VII. ER testing should be used to determine if a patient is a candidate for endocrine therapies. Per NCCN guidelines, women with Stage IV or recurrent disease characterized by tumors that are HR-positive, HER2-positive tumors have the option of receiving HER2-directed therapy as a component of their treatment plan. Options include, treatment with a HER2-targeted therapy

plus chemotherapy or endocrine therapy alone or in combination with HER2-targeted therapy. Endocrine therapy alone or in combination with HER2- targeted therapy is a less toxic approach compared with HER2-targeted therapy combined with chemotherapy. Premenopausal women treated with HER2-targeted therapy and endocrine therapy should receive ovarian suppression or ablation.

Investigational or Not Medically Necessary Uses

I. In the early stage breast cancer pivotal trial, ExteNET, subgroup analyses showed non statistically significant results for neratinib (Nerlynx) in the following populations:
   A. Breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
   B. Breast cancer that is not HR-positive
   C. Breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)

II. Neratinib (Nerlynx) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Triple negative breast cancer
   B. Breast cancer that is HER-2 negative
   C. Non-small cell lung cancer
   D. Colorectal cancer
   E. Head and neck cancer
   F. Ovarian, endometrial, uterine cancer
   G. Bladder or rectal cancer
   H. Breast cancer for greater than one year
   I. Solid tumors, other than breast cancer

References

1. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 4.2020. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/ physician_gls/pdf/breast.pdf. Updated May 8, 2020.
2. Nerlynx [Prescribing Information]. Los Angeles, CA. Puma Biotechnology, Inc. February 2020.
3. Chan PA, Delaloge S., Holmes FA. , et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2016;17(3): 367-377.
4. Puma Biotechnology, Inc. A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NALA). Available from: http://www.clinicaltrials.gov/ct2/show/NCT01808573. NLM identifier: NCT01808573.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication for advanced or metastatic breast cancer.	07/2020

Criteria transitioned to policy, with updates to newest format: inclusion of specialty provider, clarification on concurrent therapies, age requirement.	10/2019
Criteria created	09/2017