BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

NERLYNX™ (neratinib) oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Nerlynx (neratinib) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist.

2. Individual is 18 years of age or older.

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. As a single agent, for extended adjuvant treatment of patients with early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer, to following adjuvant Herceptin (trastuzumab) based therapy

b. In combination with Xeloda (capecitabine), for treatment of patients with advanced or metastatic HER2-positive breast cancer who have received two or more anti-HER2 based regimens in the metastatic setting

c. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. There is an antidiarrhea prophylactic regimen and an aggressive plan to manage diarrhea that occurs despite prophylaxis which may include additional anti-diarrheals, fluids, and electrolytes as clinically indicated

5. The individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Total bilirubin, AST, ALT, and alkaline phosphatase
   b. Negative pregnancy test in a woman of child nearing potential
   c. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

6. Individual is not using the following interacting drugs:
   a. Proton pump inhibitor such as lansoprazole, omeprazole, pantoprazole, etc.
   b. Strong CYP3A4 inhibitor such as clarithromycin, itraconazole, ketoconazole, etc.
   c. P-gp and moderate CYP3A4 dual inhibitor such as amiodarone, erythromycin, diltiazem, verapamil, etc.
   d. Strong CYP3A4 inducer such as carbamazepine, phenobarbital, phenytoin, rifampin, etc.

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Nerlynx (neratinib) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist.

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
   a. No evidence of disease progression
   b. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication.

4. Individual has not developed any other significant adverse drug effects that may exclude continued use such as:
   a. Severe diarrhea or diarrhea that recurs after maximal dose reduction
   b. Severe hepatotoxicity or hepatotoxicity that recurs after dose reduction
   c. Any life-threatening toxicity
   d. Individual who fails to recover from treatment related toxicity
   e. Toxicities that results in a treatment delay of > 3 weeks

5. Dose is at least 120 mg once daily.

6. Individual is not using the following interacting drugs:
    a. Proton pump inhibitor such as lansoprazole, omeprazole, pantoprazole, etc.
    b. Strong CYP3A4 inhibitor such as clarithromycin, itraconazole, ketoconazole, etc.
    c. P-gp and moderate CYP3A4 dual inhibitor such as amiodarone, erythromycin, diltiazem, verapamil, etc.
    d. Strong CYP3A4 inducer such as carbamazepine, phenobarbital, phenytoin, rifampin, etc.

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Nerlynx (neratinib) is indicated for the extended adjuvant treatment of adult patients with early stage), human epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy.

Breast cancer is a malignant tumor that starts either in the cells of the breast that line the ducts (known as ductal cancers) or in the lobules (lobular cancers). Breast cancer is commonly distinguished by biomarkers such as hormone receptors (HR) for estrogen (ER) and progesterone (PR) and overexpression of human epidermal growth factor receptor 2 (HER2). HER2 is subtyped as luminal B (HR+/HER2+) and HER2-enriched (HR-/HER2+). The prognosis for woman with HER2 positive breast cancer is poor, as this type grows and spreads more aggressively.

For most women, treatment of early-stage breast cancer is surgery combined with radiation therapy and oral or intravenous systemic therapy. Systemic therapy for early breast cancer includes chemotherapy, hormonal therapy, and targeted therapy. The decision of which treatment or combination of treatments to use depends on many factors, such as tumor hormone receptor type, tumor HER2 status, presence or absence of metastatic disease, patient comorbid conditions, age, and menopausal status.

The optimal duration and sequence of endocrine therapy and chemotherapy for breast cancer have not yet been established. Trastuzumab, a monoclonal antibody, is approved for the adjuvant treatment of HER2 overexpressing node positive or node negative (ER/ PR negative or with one high-risk feature) breast cancer as part of a treatment regimen with doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel or as part of a regimen with docetaxel and carboplatin or as a single agent after multi-modality anthracycline based therapy. It is also approved for metastatic breast cancer in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer and as a single agent for the treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

When used in the adjuvant setting, trastuzumab is given for 1 year following a standard chemotherapy regimen. No additional benefit has been seen in patients treated for longer than 1 year. After adjuvant trastuzumab, most woman do not receive further therapy until they experience disease recurrence. Despite adjuvant therapy, some women with HER2+ early breast cancer will have recurrences within 5 years.

The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) guidance on the treatment of patients with HER2+ breast cancer recommend the use of endocrine therapy, chemotherapy, and trastuzumab in the adjuvant setting for patients with HER2+ disease. The choice of therapy is dependent on phenotype (ER/PR/HER2), evaluation of the tumor size, location, number of lesions, and lymph node involvement, as well as the patient's health status, preferences, comorbidities, and individual risk of relapse. However, neither provide information regarding the use of biologic or targeted therapy beyond 1 year. Currently neither offers treatment recommendations for extended adjuvant setting for HER2+ breast cancer.

Neratinib is a tyrosine kinase inhibitor that irreversibly binds to epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2) and HER4. It reduces EGFR and HER2 autophosphorylation, downstream signaling pathways, and showed antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines.

Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of Nerlynx (neratinib). Additional antidiarrheal agents may be required to manage diarrhea in patients with loperamide-refractory diarrhea. Nerlynx (neratinib) dose interruptions and dose reductions may also be required to manage diarrhea.

Definitions:

Severity of diarrhea:

- Grade 1
  - Increase of < 4 stools per day over baseline
- Grade 2
  - Increase of 4-6 stools per day over baseline, lasting ≤ 5 days
- Grade 3
  - Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care and activities of daily living, lasting ≤ 2 days
- Grade 4
  - Life-threatening consequences; urgent intervention indicated

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Resources:

Nerlynx (neratinib) product information, revised by Puma Biotechnology, Inc. 03-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 04, 2022.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer Version 4.2022 – Updated June 21, 2022. Available at https://www.nccn.org. Accessed August 04, 2022.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.