BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

NERLYNX™ (neratinib) oral
Generic Equivalent (if available)

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 prior authorization 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) and/or generic equivalent (if available) 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 an individual with early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer, to following adjuvant Herceptin (trastuzumab) based therapy

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b. In combination with Xeloda (capecitabine), for treatment of an individual 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. 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, aspartate aminotransferase (AST), alanine aminotransferase (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

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. 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

7. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with:
   a. Proton pump inhibitors (e.g., lansoprazole, omeprazole, pantoprazole, others)
   b. Strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, others)
   c. P-gp and moderate CYP3A4 dual inhibitors (e.g., amiodarone, erythromycin, diltiazem, verapamil, others)
   d. Strong or moderate CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Nerlynx (neratinib) and/or generic equivalent (if available) 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 there is no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. 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 greater than 3 weeks

6. Dose is at least 120 mg once daily

7. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with:
    a. Proton pump inhibitors (e.g., lansoprazole, omeprazole, pantoprazole, others)
    b. Strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, others)
    c. P-gp and moderate CYP3A4 dual inhibitors (e.g., amiodarone, erythromycin, diltiazem, verapamil, others)
    d. Strong or moderate CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, others)

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.

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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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death related to AE
U.S. Department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Resources:

Nerlynx (neratinib) product information, revised by Puma Biotechnology, Inc. 03-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 09, 2024.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer Version 4.2024. Updated July 03, 2024. Available at https://www.nccn.org. Accessed July 09, 2024.

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.