BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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NERLYNX™ (neratinib) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Nerlynx (neratinib) is considered ***medically necessary*** and will be approved when **ALL** of 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. 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. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring 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. There are no significant interacting drugs

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Nerlynx (neratinib) is considered ***medically necessary*** and will be approved with documentation of **ALL** of the following:

  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 responded while on therapy
     a. Response is defined as:
        i. No evidence of disease progression

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ii. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

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

5. Dose is at least 120 mg once daily

6. There are no significant interacting drugs

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 a Non-cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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.

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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. 02-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on June 23, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer Version 4.2021 – Updated April 28, 2021. Available at https://www.nccn.org. Accessed on June 23, 2021.

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.