BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 9/21/17**
SECTION: DRUGS	**LAST REVIEW DATE: 9/20/18**
	LAST CRITERIA REVISION DATE: 9/20/18
	ARCHIVE DATE:

NERLYNX™ (neratinib) oral tablet

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.**

NERLYNX™ (neratinib) oral tablet (cont.)

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 an Oncologist
  2. Individual is 18 years of age or older
  3. A confirmed diagnosis of **ONE** of the following:
     - Early stage HER2-overexpressed/amplified breast cancer used as extended adjuvant treatment following 1 year of adjuvant trastuzumab based therapy
     - Recurrent brain metastases (limited or extensive) in patients with breast cancer in combination with capecitabine or in combination with paclitaxel
     - 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, 2A, or 2B
  4. Antidiarrheal prophylaxis with loperamide is initiated with first dose Nerlynx and continued during the first two cycles (56 days) of treatment
  5. There is an aggressive plan to manage diarrhea that occurs despite prophylaxis that includes additional anti-diarrheals, fluids, and electrolytes as clinically indicated
  6. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Total bilirubin, AST, ALT, and alkaline phosphatase
     - For a woman of child nearing potential there is a negative pregnancy test
  7. Woman patient of child bearing potential should use effective contraception during and for at least 1 month after therapy
  8. Woman patient who is breast feeding an infant or child should stop breast feeding during and for at least 1 month after therapy
  9. Male patient with a female partner of reproductive potential should use effective contraception during and for at least 3 months after therapy

  Initial approval duration: 6 months

NERLYNX™ (neratinib) oral tablet (cont.)

- **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. Continues to be seen by an Oncologist

  2. The condition has not worsened while on therapy
     - Worsening is define as recurrence of breast cancer

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use, such as:
     - Severe diarrhea or diarrhea that recurs after maximal dose reduction
     - Severe hepatotoxicity or hepatotoxicity that recurs after dose reduction
     - Any life-threatening toxicity
     - Individual that fails to recover from treatment related toxicity
     - Toxicities that results in a treatment delay of > 3 weeks
     - Patient unable to tolerate 120 mg once daily

  5. There are no significant interacting drugs

  Renewal duration: 12 months

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

NERLYNX™ (neratinib) oral tablet (cont.)

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 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.

Resources:

Nerlynx (neratinib). Package Insert. Revised by manufacturer 06/2018. Accessed 07-19-2018.

Nerlynx (neratinib). Package Insert. Revised by manufacturer 07-2017. Accessed 09-17-2017.

NCCN Clinical Practice Guidelines in Oncology: Breast cancer. Version 2.2017, April 6, 2017. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

NCCN Clinical Practice Guidelines in Oncology: Breast cancer. Version 1.2018, March 20, 2018. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancer. Version 1.2018, March 20, 2018. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf

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UpToDate: Systemic treatment for metastatic breast cancer: General principles. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/systemic-treatment-for-metastatic-breast-cancer-general-principles?source=search_result&search=breast%20cancer%20treatment&selectedTitle=3~150

UpToDate: Systemic treatment for HER2-positive metastatic breast cancer. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/systemic-treatment-for-her2-positive-metastatic-breast-cancer?source=see_link#H597165410

UpToDate: Adjuvant systemic therapy for HER2-positive breast cancer. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/adjuvant-systemic-therapy-for-her2-positive-breast-cancer?source=search_result&search=breast%20cancer%20treatment&selectedTitle=8~150

Denduluri N, Simerfield MR, Eisen A, et al.: Selection of Optimal Adjuvant Chemotherapy Regimens for Human Epidermal Growth Factor Receptor 2 (HER2) –Negative and Adjuvant Targeted Therapy for HER2-Positive Breast Cancers: An American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol 2016, 34 (20, July 10): 2416-2427

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.

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.