Pharmacy Policy Bulletin: J-0892 Anti-EGFR and HER2 Kinase Inhibitors - Commercial and Healthcare Reform	
Number: J-0892	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes with Prior Authorization **Quantity Limits (1., 2., 3., or 4.):** **1.** Rx Mgmt Quantity Limits = Safety/ Specialty **2.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt **3.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt + Watchful **4.** Quantity Limits = QPC = Yes **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0892-013	**Original Date:** 06/04/2003
Effective Date: 10/08/2025	**Review Date:** 09/17/2025

Drugs Product(s):	• Hernexeos (zongertinib) • Nerlynx (neratinib) • Tykerb (lapatinib) • Tukysa (tucatinib)

FDA-Approved Indication(s):	• Hernexeos (zongertinib)
	  ○ Treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have human epidermal growth factor receptor 2 (*HER2*) (epidermal growth factor receptor 2 [*ERBB2*]) tyrosine kinase domain (TKD) activating mutations, as detected by an FDA-approved test, and who have received prior systemic therapy.
	• Nerlynx (neratinib)
	  ○ As a single agent, for the extended adjuvant treatment of adult patients with early-stage *HER2*-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
	  ○ In combination with capecitabine, for the treatment of adult patients with advanced or metastatic *HER2*-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.
	• Tykerb (lapatinib)

	○ In combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors over express *HER2* and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. ○ In combination with letrozole for the treatment of postmenopausal women with hormone receptor (HR) positive metastatic breast cancer that over expresses the HER2 receptor for whom hormonal therapy is indicated. • Tukysa (tucatinib) ○ In combination with trastuzumab and capecitabine for the treatment of adult patients with advanced unresectable or metastatic *HER2*-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting. ○ In combination with trastuzumab for the treatment of adult patients with *RAS* wild-type *HER2*-positive unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

Background:	• Hernexeos is a HER2 kinase inhibitor that inhibits the phosphorylation of HER2, downstream signaling of HER2, and proliferation of lung cancer cells harboring HER2 tyrosine kinase domain activating mutations. *HER2* (also known as *ERBB2*) mutations in NSCLC are associated with poor prognosis and higher incidence of brain metastases. ○ Concomitant use of strong CYP3A inducers with Hernexeos should be avoided. If concomitant use cannot be avoided, increase the Hernexeos dose to 240 mg once daily for patients weighing < 90 kg and to 360 mg once daily for patients weighing ≥ 90 kg. • Nerlynx is a tyrosine kinase inhibitor (TKI) that irreversibly binds epidermal growth factor receptor (EGFR), HER2, and HER4. Nerlynx reduces EGFR and HER2 autophosphorylation and downstream signaling pathways. • Tykerb is a dual tyrosine kinase inhibitor against EGFR (ErbB1) and HER2 (ErbB2). Stimulation of EGFR and HER2 are associated with cell proliferation and with multiple processes involved in tumor progression, invasion, and metastasis. • Tukysa is a small molecule TKI of HER2 that shows anti-tumor activity in HER2 expressing tumor cells. In vitro, Tukysa inhibits phosphorylation of HER2 and HER3, which inhibits downstream MAPK and AKT signaling and cell proliferation. In vivo, Tukysa inhibits the growth of HER2 expressing tumors. The combination of Tukysa and trastuzumab increased anti-tumor activity in vitro and in vivo compared to either drug alone. • Anti-HER2 based regimens may include trastuzumab, lapatinib, and/or pertuzumab in combination with additional agents. • Multiple systemic therapy regimens are recommended for advanced or metastatic non-squamous NSCLC, per the National Comprehensive Cancer guidelines, including, but not limited to, pembrolizumab/carboplatin or cisplatin/pemetrexed; cemiplimab-rwlc/pemetrexed/carboplatin or cisplatin; atezolizumab/carboplatin/paclitaxel/bevacizumab; nivolumab/ipilimumab/pemetrexted/carboplatin or cisplatin. • The Oncomine Dx Target Test (Life Technologies Corporation) is an FDA-approved companion diagnostic test for identifying patients who may be eligible for treatment with Hernexeos. For additional information regarding FDA-approved companion diagnostics, please visit: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

	• Prescribing Considerations
	  ○ Kinase inhibitors should be prescribed under the supervision of a hematologist/oncologist.
	  ○ Tykerb has a black box warning for hepatotoxicity.

Approval Criteria

I. Initial Authorization

A. Hernexeos (zongertinib)

When a benefit, coverage of Hernexeos may be approved when all of the following criteria are met **(1. through 4.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of unresectable or metastatic non-squamous non-small cell lung cancer (ICD-10: C34.90).
3. Disease harbors *HER2 (ERBB2)* tyrosine kinase domain activating mutations, as detected by an FDA-approved test.
4. The member has received prior systemic therapy.

B. Nerlynx (neratinib)

When a benefit, coverage of Nerlynx may be approved when all of the following criteria are met **(1. and 2.)**:

1. The member is 18 years of age or older.
2. The member meets one (1) of the following criteria **(a. or b.)**:
  a. The member has a diagnosis of early-stage, *HER2*-positive breast cancer (ICD-10: C50) and meets all of the following criteria **(i. and ii.)**:
    i. The member will be using Nerlynx as a single agent.
    ii. The member has received adjuvant trastuzumab-based therapy.
  b. The member has a diagnosis of advanced *HER2*-positive or metastatic *HER2*-positive breast cancer (ICD-10: C50) and meets all of the following criteria **(i. and ii.)**:
    i. The member will be using Nerlynx in combination with capecitabine.
    ii. The member has received two (2) or more prior anti-*HER2* based regimens in the metastatic setting.

C. Tykerb (lapatinib)

When a benefit, coverage of Tykerb (lapatinib) may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is 18 years of age or older.
2. The member meets one (1) of the following criteria **(a. or b.)**:
  a. The member will be using Tykerb in combination with capecitabine and meets all of the following criteria **(i. and ii.)**:
    i. The member meets one (1) of the following criteria **(A) or B))**:
      A) Disease is classified as advanced *HER2*-positive breast cancer (ICD-10: C50)
      B) Disease is classified as metastatic *HER2*-positive breast cancer (ICD-10: C50)
    ii. The member has received prior therapy including all of the following **(A), B), and C))**:
      A) An anthracycline
      B) A taxane
      C) Trastuzumab
  b. The member will be using Tykerb in combination with letrozole and meets all of the following criteria **(i., ii., and iii.)**:
    i. The member is post-menopausal.
    ii. The member has a diagnosis of hormone receptor-positive metastatic breast cancer (ICD-10: C50)
    iii. The member's cancer overexpresses the HER2 receptor.

3. If the request is for brand Tykerb, the member has experienced therapeutic failure or intolerance to generic lapatinib.

D. Tukysa (tucatinib)

1. **Breast Cancer** (ICD-10: C50)
   When a benefit, coverage of Tukysa may be approved when all of the following criteria are met **(a. through d.):**
   - **a.** The member is 18 years of age or older.
   - **b.** The member has a diagnosis of one (1) of the following **(i. or ii.)**:
     - **i.** Advanced unresectable *HER2*-positive breast cancer.
     - **ii.** Metastatic *HER2*-positive breast cancer.
   - **c.** The member will be using Tukysa in combination with trastuzumab and capecitabine.
   - **d.** The member has received one (1) or more prior anti-*HER2* based regimens in the metastatic setting.

2. **Colorectal Cancer** (ICD-10: C19)
   When a benefit, coverage of Tukysa may be approved when all of the following criteria are met **(a. through d.):**
   - **a.** The member is 18 years of age or older.
   - **b.** The member has a diagnosis of colorectal cancer and meets all of the following criteria **(i. and ii.):**
     - **i.** Disease is *RAS*-wild type, *HER2*-positive.
     - **ii.** Disease is unresectable or metastatic.
   - **c.** The member will be using Tukysa in combination with trastuzumab.
   - **d.** The member has experienced disease progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

II. Reauthorization

When a benefit, reauthorization may be approved when all of the following criteria are met **(A. and B.)**:

- **A.** The prescriber attests that the member is tolerating therapy and has experienced a therapeutic response defined as either one (1) of the following **(1. or 2.)**:
  - **1.** Disease improvement
  - **2.** Delayed disease progression
- **B.** If the request is for brand Tykerb, documentation that the AB-rated generic is ineffective or not tolerated.

III. Quantity Limits

A. Hernexeos

When a benefit, additional quantities of Hernexeos may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is taking a strong CYP3A inducer.
2. The prescriber attests to the member's weight.
3. For requests exceeding the coded quantity limit, Hernexeos may be authorized in quantities as follows:

Coded Quantity Limit	Patient Weight	Approvable Quantity
300 tablets per 90 days	< 90 kg	360 tablets per 90 days
	≥ 90 kg	540 tablets per 90 days

IV. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

V. Coverage of oncology medications listed in this policy may be approved on a case-by-case basis per indications supported in the most current NCCN guidelines.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support their effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None
Refer to J-699 and J-611 for previous versions.

References:

1. Hernexeos [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; August 2025.
2. Nerlynx [package insert]. Los Angeles, CA: Puma Biotechnology; June 2021.
3. Tykerb [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2022.
4. Tukysa [package insert]. Bothell, WA: Seattle Genetics, Inc.; January 2023.
5. National Comprehensive Cancer Network. NCCN Guidelines Version 8.2025 Non-Small Cell Lung Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 18, 2025.