Evolent Clinical Guideline 3073 for Trastuzumab Products, Pertuzumab, and Phesgo

Guideline Number:	Applicable Codes	
Evolent_CG_3073		
"Evolent" refers to Evolent Health LLC and Evolent Specialty Services, Inc. 		
Original Date:	**Last Revised Date:**	**Implementation Date:**
July 2011	April 2025	April 2025

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STATEMENT

Purpose

To define and describe the accepted indications for Trastuzumab products [Herceptin (trastuzumab), Herceptin Hylecta (trastuzumab hyaluronidase), Ogivri (trastuzumab-dkst), Herzuma (trastuzumab-pkrb), Ontruzant (trastuzumab-dttb), Kanjinti (trastuzumab-anns), Trazimera (trastuzumab-qyyp), Hercessi (trastuzumab-strf)], Pertuzumab (pertuzumab), and Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

HER-2 Positive Breast Cancer

- The member has: 1) node positive and/or tumor stage ≥ T2 HER-2 positive breast cancer OR 2) node negative (N0) and tumor stage T1 HER-2 positive breast cancer, AND trastuzumab/trastuzumab biosimilar +/- Perjeta (pertuzumab) may be used as neoadjuvant treatment OR as adjuvant treatment in members who did not receive neoadjuvant therapy. The following chemotherapy regimens are acceptable for use with trastuzumab/trastuzumab biosimilar +/- Perjeta (pertuzumab) combination therapy as neoadjuvant or adjuvant treatment:
    - Trastuzumab/trastuzumab biosimilar +/- Perjeta (pertuzumab) with paclitaxel following AC (doxorubicin + cyclophosphamide)
    - Trastuzumab/trastuzumab biosimilar +/- Perjeta (pertuzumab) with docetaxel following AC (doxorubicin + cyclophosphamide)
    - Trastuzumab/trastuzumab biosimilar +/- Perjeta(pertuzumab) with docetaxel/paclitaxel
    - TCH (docetaxel, carboplatin, and trastuzumab/trastuzumab biosimilar) +/- Perjeta (pertuzumab)

- Trastuzumab/trastuzumab biosimilar with docetaxel and cyclophosphamide.

OR

- Trastuzumab/trastuzumab biosimilar +/- Perjeta (pertuzumab) may be used as continuation neoadjuvant/adjuvant therapy following neoadjuvant/adjuvant trastuzumab/trastuzumab biosimilar +/- Perjeta (pertuzumab) + Chemotherapy OR
- Trastuzumab/trastuzumab biosimilar may be used as first line or subsequent line therapy, with or without Perjeta (pertuzumab) for recurrent or metastatic HER-2 positive breast cancer:
  - In combination with Novaldex (tamoxifen), Faslodex (fulvestrant), or an aromatase inhibitor for a member whose disease is also ER/PR positive OR
  - In combination with pertuzumab and a Taxane [Taxotere (docetaxel) or Taxol (paclitaxel)] regardless of the ER/PR status OR
  - In combination with other single agent chemotherapy agents e.g., vinorelbine.

OR

- In combination with Tukysa (tucatinib) + Xeloda (capecitabine) for members with metastatic HER-2 positive breast cancer and brain metastases OR in members without brain metastases if there is disease progression on one or more prior lines of anti-HER-2 therapy in the metastatic setting.

HER-2 Positive Gastric/Esophageal and Esophagogastric Junction Cancers

- The member has a diagnosis of recurrent/metastatic gastric or esophageal or esophagogastric junction cancer and the cancer is HER-2 positive (defined as IHC 3+ or FISH/ISH positive) AND
- Trastuzumab/trastuzumab biosimilar is being used in combination with cisplatin or oxaliplatin and 5-fluorouracil (or capecitabine), with or without Keytruda (pembrolizumab) as first line therapy.

CONTRAINDICATIONS/WARNINGS

- Contraindications
  - Pertuzumab
    - Known hypersensitivity to pertuzumab or any component of the formulation
  - Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf)
    - Known hypersensitivity to pertuzumab, trastuzumab, or hyaluronidase, or any component of the formulation
- US Boxed Warning
  - Trastuzumab/trastuzumab biosimilar
    - Cardiomyopathy
      - Trastuzumab administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving

trastuzumab with anthracycline-containing chemotherapy regimens.

- Evaluate left ventricular function in all patients prior to and during treatment with trastuzumab. Discontinue trastuzumab treatment in patients receiving adjuvant therapy, and withhold trastuzumab in patients with metastatic disease for clinically significant decrease in left ventricular function.

- Infusion reactions and pulmonary toxicity
  - Trastuzumab administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of trastuzumab administration. Interrupt trastuzumab infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue trastuzumab for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.
- Pregnancy
  - Exposure to trastuzumab during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception.

- Pertuzumab
  - Cardiotoxicity
    - Pertuzumab can result in subclinical and clinical cardiac failure manifesting as decreased left ventricular ejection fraction (LVEF) and congestive heart failure (CHF). Evaluate cardiac function prior to and during treatment. Discontinue pertuzumab treatment for a confirmed clinically significant decrease in left ventricular function.
  - Pregnancy
    - Exposure to pertuzumab can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception.
- Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf)
  - Cardiomyopathy
    - Pertuzumab/trastuzumab/hyaluronidase administration can result in subclinical and clinical cardiac failure. The incidence and severity were highest in patients receiving pertuzumab/trastuzumab/hyaluronidase with anthracycline-containing chemotherapy regimens. Evaluate cardiac function prior to and during treatment with pertuzumab/trastuzumab/hyaluronidase. Discontinue pertuzumab/trastuzumab/hyaluronidase treatment in patients receiving adjuvant therapy and withhold pertuzumab/trastuzumab/hyaluronidase in patients with metastatic disease for clinically significant decrease in left ventricular function.
  - Embryo-fetal toxicity
    - Exposure to pertuzumab/trastuzumab/hyaluronidase can result in embryo-fetal death and birth defects, including oligohydramnios and

oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception.

- Pulmonary toxicity
  - Pertuzumab/trastuzumab/hyaluronidase administration can result in serious and fatal pulmonary toxicity. Discontinue pertuzumab/trastuzumab/hyaluronidase for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve.

EXCLUSION CRITERIA

- Trastuzumab/trastuzumab biosimilar use in gastric or gastroesophageal junction cancer after disease progression with first line therapy containing trastuzumab.
- Continuation of trastuzumab/trastuzumab biosimilar after disease progression on trastuzumab-based therapy in HER-2 positive esophageal, gastroesophageal, and gastric adenocarcinomas.
- Dosing exceeds single dose limit of trastuzumab/trastuzumab biosimilar 8 mg/kg for the loading dose, 6mg/kg for subsequent doses when given every 3 weeks; 4 mg/kg for the loading dose and 2 mg/kg for the subsequent doses, when trastuzumab/trastuzumab biosimilar is being given weekly.
- Dosing exceeds single dose limit of Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) 1,200 mg (initial dose) and 600 mg (subsequent dose).
- Dosing exceeds single dose limit of Perjeta (pertuzumab) 840 mg initially then 420 mg every 3 weeks.
- Total treatment duration exceeds a maximum 52 weeks or 1 year (the equivalent of 17 three-week cycles) in non-metastatic HER-2 positive breast cancer. The above duration does not include any necessary therapy interruption, e.g., due to breast surgery and post-operative recovery.
- Investigational use of Trastuzumab/Trastuzumab biosimilar/Pertuzumab/Phesgo with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
  - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
  - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
  - Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example,

in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).

- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J9306 - Injection, pertuzumab, 1 mg
- J9316 - Injection, pertuzumab, trastuzumab, and hyaluronidase-zzxf, per 10 mg
- J9355 - Injection, trastuzumab, excludes biosimilar, 10 mg
- J9356 - Injection, trastuzumab, 10 mg and hyaluronidase-oysk
- Q5112 - Injection, trastuzumab-dttb, biosimilar, (ontruzant), 10 mg
- Q5113 - Injection, trastuzumab-pkrb, biosimilar, (herzuma), 10 mg
- Q5114 - Injection, trastuzumab-dkst, biosimilar, (ogivri), 10 mg
- Q5116 - Injection, trastuzumab-qyyp, biosimilar, (trazimera), 10 mg
- Q5117 - Injection, trastuzumab-anns, biosimilar, (kanjinti), 10 mg
- Q5146 - Injection, trastuzumab-strf (hercessi), biosimilar, 10 mg

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary

April 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1134 Trastuzumab Products, Pertuzumab, and Phesgo • Updated breast cancer indication to allow for “T1, N0” stage to receive trastuzumab/trastuzumab biosimilar +/- pertuzumab containing regimens • Updated exclusion criteria • Updated references
June 2024	• Added new biosimilar “Hercessi (trastuzumab-strf)” to guideline • Added new reference • Updated NCH verbiage to Evolent

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Murthy RK, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med*. 2020 Feb 13;382(7):597-609. doi: 10.1056/NEJMoa1914609.
2. Gianni L, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016 Jun;17(6):791-800. doi: 10.1016/S1470-2045(16)00163-7.
3. Piccart M, et al; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. *J Clin Oncol*. 2021 May 1;39(13):1448-1457. doi: 10.1200/JCO.20.01204.
4. von Minckwitz G, et al; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med*. 2019 Feb 14;380(7):617-628. doi: 10.1056/NEJMoa1814017.
5. von Minckwitz G, et al; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med*. 2017 Jul 13;377(2):122-131. doi: 10.1056/NEJMoa1703643.
6. Phesgo prescribing information. Genentech, Inc. South San Francisco, CA 2024.
7. Perjeta prescribing information. Genentech, Inc. South San Francisco, CA 2021.
8. Herceptin Hylecta prescribing information. Genentech, Inc. South San Francisco, CA 2024.
9. Herceptin prescribing information. Genentech, Inc. South San Francisco, CA 2024.
10. Trazimera prescribing information. Pfizer Ireland Pharmaceuticals. Cork, Ireland 2020
11. Ogivri prescribing information. Biocon Biologics Inc. Cambridge, MA 2024.
12. Ontruzant prescribing information. Samsung Bioepis Co., Ltd. Incheon, 21987, Republic of Korea 2025
13. Herzuma prescribing information. Teva Pharmaceuticals USA, Inc. North Wales, PA 2024
14. Kanjinti prescribing information. Amgen Inc. Thousand Oaks, CA 2024.
15. Hercessi prescribing information. Accord BioPharma Inc. Raleigh, NC 2024.
16. Clinical Pharmacology Elsevier Gold Standard 2025.
17. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2025.
18. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2025.
19. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2025.
20. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
21. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
22. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.