

Herceptin Hylecta® (trastuzumab and hyaluronidase-oysk)(Subcutaneous)

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I. Length of Authorization ¹

Coverage is provided for 6 months and may be renewed (unless otherwise specified).

- Adjuvant therapy may be authorized for a total of fifty-two (52) weeks.

II. Dosing Limits

Max Units (per dose and over time) [HCPCS Unit]:

- 60 billable units every 21 days

III. Initial Approval Criteria ¹⁻⁵

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria

- Left ventricular ejection fraction (LVEF) is within normal limits prior to initiating therapy and will be assessed at regular intervals (e.g., every 3 months) during treatment; **AND**
- Patient has cancer is human epidermal growth factor receptor 2 (HER2)-positive* disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Females of reproductive potential have a negative pregnancy test prior to initiating treatment and will use effective contraception during treatment and for 7 months after the last dose; **AND**
- Therapy will not be substituted with or for ado-trastuzumab emtansine (Kadcyla) or fam-trastuzumab deruxtecan-nxki (Enhertu); **AND**
- Therapy will not be used in combination with intravenous chemotherapy agents; **AND**
- Therapy will not be used in combination with trastuzumab (or any of its biosimilar products) or pertuzumab/trastuzumab and hyaluronidase-zzxf (Phesgo); **AND**

Breast Cancer** † 1

- Used as adjuvant therapy; **AND**
 - Patient has \geq T1 disease, node positive disease, or inflammatory disease (unless otherwise specified); **AND**
 - Used as a single agent following anthracycline-based therapy †; **OR**
- Used for metastatic disease; **AND**
 - Used as a single agent in patients who have received one or more prior chemotherapy regimens for metastatic disease †

****NOTE:** Coverage for Herceptin Hylecta will NOT encompass all FDA approved indications. Coverage will be ONLY provided when the above criteria is met.

FDA approved indications:

Adjuvant treatment of adults with HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy

Metastatic treatment of adults:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

*HER2-positive overexpression criteria: 6,7

Immunohistochemistry (IHC) assay 3+; **OR**

- Dual-probe in situ hybridization (ISH) assay HER2/CEP17 ratio \geq 2.0 AND average HER2 copy number \geq 4.0 signals/cell; **OR**
- Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
 - HER2/CEP17 ratio \geq 2.0 AND average HER2 copy number $<$ 4.0 signals/cell AND concurrent IHC 3+; **OR**
 - HER2/CEP17 ratio $<$ 2.0 AND average HER2 copy number \geq 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**
 - HER2/CEP17 ratio $<$ 2.0 AND average HER2 copy number \geq 4.0 and $<$ 6.0 signals/cell AND concurrent IHC 3+

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

❖ If confirmed using an immunotherapy assay - <http://www.fda.gov/companiondiagnostics>

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Ⓞ Orphan Drug

IV. Renewal Criteria ¹

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Duration of authorization has not been exceeded (*refer to Section I*); **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: cardiotoxicity (e.g., left ventricular dysfunction, cardiomyopathy, etc.), pulmonary toxicity (e.g., dyspnea, interstitial pneumonitis, etc.), neutropenia, severe administration-related reactions (e.g., hypersensitivity, anaphylaxis), etc.; **AND**
- Left ventricular ejection fraction (LVEF) within the previous 3 months as follows:
 - LVEF is within the institutional normal limits, and has not had an absolute decrease of $\geq 16\%$ from pre-treatment baseline; **OR**
 - LVEF is below the institutional lower limits of normal, and has not had an absolute decrease of $\geq 10\%$ from pre-treatment baseline

V. Dosage/Administration ¹

| Indication | Dose |
|---|--|
| Breast Cancer | Administer 600 mg trastuzumab and 10,000 units hyaluronidase subcutaneously every three weeks. <ul style="list-style-type: none"> ○ Adjuvant therapy: administer for 52 weeks or until disease recurrence ○ Metastatic breast cancer: administer until disease progression |
| Note: – To be administered by a health care professional for subcutaneous use only in the thigh. Do not administer intravenously. | |

VI. Billing Code/Availability Information

HCPSC Code:

- J9356 – Injection, trastuzumab, 10 mg and hyaluronidase-oysk; 1 billable unit = 10 mg

NDC:

- Herceptin Hylecta 600 mg/10,000 units (providing 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL) single-dose vials: 50242-0077-xx

VII. References (STANDARD)

1. Herceptin Hylecta [package insert]. South San Francisco, CA; Genentech, Inc; June 2024. Accessed July 2025.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) trastuzumab and hyaluronidase human. National Comprehensive Cancer Network, 2025. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed July 2025.
3. Jackisch C, Stroyakovskiy D, Pivot X, et al. Subcutaneous vs Intravenous Trastuzumab for Patients With ERBB2-Positive Early Breast Cancer: Final Analysis of the HannaH Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2019 May 1;5(5):e190339.
4. Gligorov J, Ataseven B, Verrill M, et al. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. *Eur J Cancer*. 2017 Sep;82:237-246.
5. Pivot X, Verma S, Fallowfield L, et al. Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: Final analysis of the randomised, two-cohort PrefHer study. *Eur J Cancer*. 2017 Nov;86:82-90.
6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer 4.2025. National Comprehensive Cancer Network, 2025. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed July 2025.
7. Wolff AC, Hammond EH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *J Clin Oncol* 2018;36:2105-2122.

VIII. References (ENHANCED)

- 1e. Woodward N, De Boer RH, Redfern A, et al. Results From the First Multicenter, Open-label, Phase IIIb Study Investigating the Combination of Pertuzumab With Subcutaneous Trastuzumab and a Taxane in Patients With HER2-positive Metastatic Breast Cancer (SAPPHIRE). *Clin Breast Cancer*. 2019;19(3):216–224. doi:10.1016/j.clbc.2019.02.008.
- 2e. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005 Oct 20;353(16):1659-72.

- 3e. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007 Jan 6;369(9555):29-36.
- 4e. Prime Therapeutics Management. Trastuzumab SQ Clinical Literature Review Analysis. Last updated July 2025. Accessed July 2025.

Appendix 1 – Covered Diagnosis Codes

| ICD-10 | ICD-10 Description |
|---------|---|
| C50.011 | Malignant neoplasm of nipple and areola, right female breast |
| C50.012 | Malignant neoplasm of nipple and areola, left female breast |
| C50.019 | Malignant neoplasm of nipple and areola, unspecified female breast |
| C50.021 | Malignant neoplasm of nipple and areola, right female breast |
| C50.022 | Malignant neoplasm of nipple and areola, left female breast |
| C50.029 | Malignant neoplasm of nipple and areola, unspecified female breast |
| C50.111 | Malignant neoplasm of central portion of right female breast |
| C50.112 | Malignant neoplasm of central portion of left female breast |
| C50.119 | Malignant neoplasm of central portion of unspecified female breast |
| C50.121 | Malignant neoplasm of central portion of right male breast |
| C50.122 | Malignant neoplasm of central portion of left male breast |
| C50.129 | Malignant neoplasm of central portion of unspecified male breast |
| C50.211 | Malignant neoplasm of upper-inner quadrant of right female breast |
| C50.212 | Malignant neoplasm of upper-inner quadrant of left female breast |
| C50.219 | Malignant neoplasm of upper-inner quadrant of unspecified female breast |
| C50.221 | Malignant neoplasm of upper-inner quadrant of right male breast |
| C50.222 | Malignant neoplasm of upper-inner quadrant of left male breast |
| C50.229 | Malignant neoplasm of upper-inner quadrant of unspecified male breast |
| C50.311 | Malignant neoplasm of lower-inner quadrant of right female breast |
| C50.312 | Malignant neoplasm of lower-inner quadrant of left female breast |
| C50.319 | Malignant neoplasm of lower-inner quadrant of unspecified female breast |
| C50.321 | Malignant neoplasm of lower-inner quadrant of right male breast |
| C50.322 | Malignant neoplasm of lower-inner quadrant of left male breast |
| C50.329 | Malignant neoplasm of lower-inner quadrant of unspecified male breast |
| C50.411 | Malignant neoplasm of upper-outer quadrant of right female breast |
| C50.412 | Malignant neoplasm of upper-outer quadrant of left female breast |

| ICD-10 | ICD-10 Description |
|---------|---|
| C50.419 | Malignant neoplasm of upper-outer quadrant of unspecified female breast |
| C50.421 | Malignant neoplasm of upper-outer quadrant of right male breast |
| C50.422 | Malignant neoplasm of upper-outer quadrant of left male breast |
| C50.429 | Malignant neoplasm of upper-outer quadrant of unspecified male breast |
| C50.511 | Malignant neoplasm of lower-outer quadrant of right female breast |
| C50.512 | Malignant neoplasm of lower-outer quadrant of left female breast |
| C50.519 | Malignant neoplasm of lower-outer quadrant of unspecified female breast |
| C50.521 | Malignant neoplasm of lower-outer quadrant of right male breast |
| C50.522 | Malignant neoplasm of lower-outer quadrant of left male breast |
| C50.529 | Malignant neoplasm of lower-outer quadrant of unspecified male breast |
| C50.611 | Malignant neoplasm of axillary tail of right female breast |
| C50.612 | Malignant neoplasm of axillary tail of left female breast |
| C50.619 | Malignant neoplasm of axillary tail of unspecified female breast |
| C50.621 | Malignant neoplasm of axillary tail of right male breast |
| C50.622 | Malignant neoplasm of axillary tail of left male breast |
| C50.629 | Malignant neoplasm of axillary tail of unspecified male breast |
| C50.811 | Malignant neoplasm of overlapping sites of right female breast |
| C50.812 | Malignant neoplasm of overlapping sites of left female breast |
| C50.819 | Malignant neoplasm of overlapping sites of unspecified female breast |
| C50.821 | Malignant neoplasm of overlapping sites of right male breast |
| C50.822 | Malignant neoplasm of overlapping sites of left male breast |
| C50.829 | Malignant neoplasm of overlapping sites of unspecified male breast |
| C50.911 | Malignant neoplasm of unspecified site of right female breast |
| C50.912 | Malignant neoplasm of unspecified site of left female breast |
| C50.919 | Malignant neoplasm of unspecified site of unspecified female breast |
| C50.921 | Malignant neoplasm of unspecified site of right male breast |
| C50.922 | Malignant neoplasm of unspecified site of left male breast |
| C50.929 | Malignant neoplasm of unspecified site of unspecified male breast |
| Z85.3 | Personal history of malignant neoplasm of breast |

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

| Medicare Part B Administrative Contractor (MAC) Jurisdictions | | |
|---|---|---|
| Jurisdiction | Applicable State/US Territory | Contractor |
| E (1) | CA, HI, NV, AS, GU, CNMI | Noridian Healthcare Solutions, LLC |
| F (2 & 3) | AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ | Noridian Healthcare Solutions, LLC |
| 5 | KS, NE, IA, MO | Wisconsin Physicians Service Insurance Corp (WPS) |
| 6 | MN, WI, IL | National Government Services, Inc. (NGS) |
| H (4 & 7) | LA, AR, MS, TX, OK, CO, NM | Novitas Solutions, Inc. |
| 8 | MI, IN | Wisconsin Physicians Service Insurance Corp (WPS) |
| N (9) | FL, PR, VI | First Coast Service Options, Inc. |
| J (10) | TN, GA, AL | Palmetto GBA |
| M (11) | NC, SC, WV, VA (excluding below) | Palmetto GBA |
| L (12) | DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA) | Novitas Solutions, Inc. |
| K (13 & 14) | NY, CT, MA, RI, VT, ME, NH | National Government Services, Inc. (NGS) |
| 15 | KY, OH | CGS Administrators, LLC |