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

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Document Number: IC-0544

Last Review Date: 05/03/2021
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I. Length of Authorization

Coverage is provided for six months and may be renewed.

- Use in the adjuvant setting is limited to a total of 52 weeks of treatment.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

– Herceptin Hylecta 600 mg/10,000 units single-dose vial: 1 vial every 21 days

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

Breast Cancer

- 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**
- Therapy will not be substituted with or for ado-trastuzumab emtansine (Kadcyla) or fam-trastuzumab deruxtecan-nxki (Enhertu); **AND**
- Will not be used in combination with intravenous chemotherapy agents; **AND**
- Will not be used in combination with trastuzumab (or any of its biosimilar products [e.g., Ogivri, Kanjinti, Trazimera, Herzuma, Ontruzant]) or pertuzumab/trastuzumab and hyaluronidase-zzxf (Phesgo); **AND**

Breast Cancer** †

- Used as adjuvant therapy as a single agent following anthracycline-based therapy †; **OR**
- Used for metastatic disease as a single agent in patients who have received one or more prior treatments 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 ≥ 2.0 AND average HER2 copy number ≥ 4.0 signals/cell; **OR**
• Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
  ○ HER2/CEP17 ratio ≥ 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 ≥ 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**
  ○ HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 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)

IV. Renewal Criteria [1]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **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 the following: 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); **AND**
    - LVEF is within the institutional normal limits, but has not had an absolute decrease of ≥ 16% from pre-treatment baseline (LVEF results must be within the previous 3 months); **OR**
    - LVEF is below the institutional lower limits of normal, but has not had an absolute decrease of ≥ 10% from pre-treatment baseline (LVEF results must be within the previous 3 months); **AND**
- For the adjuvant treatment of breast cancer, the patient has not exceeded a maximum of 52 weeks of therapy

V. Dosage/Administration

Indication	Dose
Breast Cancer	Administer* 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) subcutaneously over approximately 2-5 minutes once every three weeks. o Adjuvant therapy should be continued for 52 weeks or until disease recurrence o Metastatic breast cancer should be treated until disease progression ** Herceptin Hylecta should be administered by healthcare professional.*

VI. Billing Code/Availability Information

HCPCS 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; February 2019. Accessed April 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) trastuzumab and hyaluronidase human. National Comprehensive Cancer Network, 2021. 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 April 2021.
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 3.2021. National Comprehensive Cancer Network, 2021. 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 April 2021.
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.
8. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Trastuzumab – Trastuzumab Biologics (A56660). Centers for Medicare & Medicaid Services, Inc. Updated on 02/05/2021 with effective date of 01/01/2021. Accessed April 2021.

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. Magellan Health, Magellan Rx Management. Trastuzumab SQ Clinical Literature Review Analysis. Last updated April 2021. Accessed April 2021.

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

ICD-10	ICD-10 Description
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
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

ICD-10	ICD-10 Description
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

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

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 Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

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

Jurisdiction(s): N (9)	**NCD/LCD/LCA Document (s):** A56660
https://www.cms.gov/medicare-coverage-database/search/document-id-search-results.aspx?Date=10/30/2019&DocID=A56660&bc=hAAAAAAAAAAA&	

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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
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

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; pCR = pathological complete response

Breast Cancer (HER2-Positive)

Adjuvant Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trastuzumab SQ	2A	Yes	Phase 3 (HannaH Study), open-label, multi-center	Trastuzumab IV	pCR	Neoadjuvant and adjuvant therapy	• Final analysis of the HannaH trial further confirms the comparable efficacy and safety of subcutaneous and intravenous trastuzumab and highlights the suitability of subcutaneous trastuzumab as an alternative route of administration for patients with HER2-positive early breast cancer.
Trastuzumab SQ	2A	Yes	Phase 3 (SafeHER Study)	N/A	Safety Tolerability	Adjuvant therapy	• SafeHer confirms the safety and tolerability of the trastuzumab SQ given as 600 mg fixed dose for 1 year (every 3 weeks for 18 cycles) as adjuvant therapy with concurrent or sequential chemotherapy for HER2-positive early breast cancer.
Treatment naïve metastatic breast cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Trastuzumab SQ + pertuzumab + taxane	2A	No	Phase 3 (SAPPHIRE), open-label, non-randomized	N/A	Safety Tolerability	First-line for metastatic breast cancer	• Safety and efficacy appear similar to previous studies of intravenous trastuzumab in this combination.