CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Trastuzumab and Hyaluronidase-oysk (Herceptin Hylecta®)

Version: 1.0

Effective Date: 4/1/2026

NantHealth® | Eviti®

Please note the following:

For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Trastuzumab and Hylaluronidase-oysk (Herceptin Hylecta®)

Discussion

Trastuzumab is a monoclonal antibody specifically designed to target human epidermal growth factor receptor 2 (HER2) receptors, which are transmembrane protein receptors on both normal cells and HER2+ tumor cells. HER2 plays an important role in the signaling network that drives cell growth. Trastuzumab blocks intracellular signaling pathways which may promote cell death and arrest cell growth.[1] Hyaluronidase (recombinant human) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Common adverse reactions include fatigue, arthralgia, diarrhea, injection site reaction, upper respiratory tract infection, rash, myalgia, nausea, headache, edema, flushing, pyrexia, cough, pain in extremity, fever, chills, infection, congestive heart failure, and insomnia. Clinically significant adverse reactions include cardiomyopathy, embryo-fetal toxicity, pulmonary toxicity, exacerbation of chemotherapy-induced neutropenia, and hypersensitivity and administration-related reactions (including anaphylaxis).

Trastuzumab and hyaluronidase-oysk is approved by the Food and Drug Administration (FDA)[2] and endorsed by the National Comprehensive Cancer Network (NCCN) for breast cancer.[3]

Definitions

- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[4]
- **Human Epidermal Growth Factor Receptor (HER2)** - A targetable transmembrane glycoprotein receptor of the epidermal growth factor receptor (EGFR) family. It plays a crucial role in cell proliferation, survival, and differentiation.[5]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of over 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.[6]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when all criteria are met:

Breast Cancer

1. At least 18 years of age; AND

2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) disease for one of the following:
   a) As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
   b) As part of a treatment regimen with docetaxel and carboplatin
   c) Single agent therapy following multi-modality anthracycline based therapy; OR
4. Metastatic breast cancer for one of the following:
   a) In combination with paclitaxel for first-line treatment of HER2-overexpressing disease
   b) Single agent for treatment of HER2-overexpressing disease after receiving one or more chemotherapy regimens for metastatic disease;[2] OR

Inflammatory Breast Cancer

For **NCCN** required criteria coverage:

5. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive disease for one of the following:
   a) Component of TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) regimen
   b) In combination with docetaxel with or without pertuzumab following AC regimen
   c) In combination with paclitaxel, carboplatin and pertuzumab
   d) In combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   e) In combination with paclitaxel and pertuzumab following AC regimen (dose-dense or every 3 weeks)
   f) In combination with docetaxel and cyclophosphamide
   g) In combination with paclitaxel and pertuzumab
   h) In combination with docetaxel and pertuzumab

   Note: It is acceptable to change administration sequence to taxane followed by AC; OR

6. Adjuvant systemic therapy if response to preoperative systemic therapy, followed by surgery, and need to complete planned chemotherapy, for HER2-positive tumors for one of the following:
   a) In combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   b) In combination with docetaxel following AC regimen
   c) In combination with paclitaxel, carboplatin and pertuzumab for pT2-3 and pN0 or pN+ tumors only
   d) In combination with docetaxel and cyclophosphamide
   e) Component of TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab) regimen (preferred regimen) for pT2-3 and pN0 or pN+ tumors only
   f) In combination with pertuzumab and paclitaxel following AC regimen (dose-dense or every 3 weeks) for pT2-3 and pN0 or pN+ tumors only

g) In combination with pertuzumab and docetaxel following AC regimen for pT2-3 and pN0 or pN+ tumors only
h) In combination with paclitaxel and pertuzumab for pT2-3 and pN0 or pN+ tumors only
i) Component of TCH (docetaxel, carboplatin, and trastuzumab) regimen
j) In combination with docetaxel and pertuzumab
k) In combination with paclitaxel for low-risk T1, N0, M0, HER2-positive tumors particularly for patients not eligible for other standard adjuvant regimens due to comorbidities

Notes:
1. It is acceptable to change administration sequence to taxane followed by AC
2. If no residual disease after preoperative therapy or no preoperative therapy, complete up to one year of HER2 targeted therapy with trastuzumab with or without pertuzumab after completing planned chemotherapy regimen course. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used; OR

7. Treatment of patients with no response to preoperative systemic therapy or recurrent unresectable (local or regional) or stage IV (M1) hormone receptor-positive HER2-positive disease in postmenopausal women or premenopausal women treated with (or without if used with tamoxifen) ovarian ablation/suppression in one of the following:
   a) In combination with tamoxifen
   b) In combination with fulvestrant
   c) In combination with aromatase inhibition with or without lapatinib
   d) First-line therapy in combination with an aromatase inhibitor and pertuzumab with or without palbociclib
   e) Fourth-line therapy and beyond in combination with abemaciclib and fulvestrant

   Note: Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis; OR

8. For no response to preoperative systemic therapy, or recurrent unresectable (local or regional) or stage IV (M1) HER2-positive disease that is either hormone receptor-negative, or hormone receptor-positive with or without endocrine therapy for one of the following:
   a) First-line therapy in combination with pertuzumab with either docetaxel or paclitaxel
   b) Fourth-line therapy and beyond in combination with docetaxel, vinorelbine, or capecitabine, or with paclitaxel with or without carboplatin
   c) Fourth-line therapy and beyond in combination with cyclophosphamide, eribulin, gemcitabine, ixabepilone, lapatinib (without cytotoxic therapy), or albumin-bound paclitaxel
   d) In combination with pertuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab; OR
9. Second or third-line therapy and beyond in combination with capecitabine and tucatinib (preferred in patients with both systemic and CNS progression in the third-line setting and beyond) for patients with no response to preoperative systemic therapy, or recurrent

unresectable (local or regional) or stage IV (M1) human epidermal growth factor receptor 2 (HER2)-positive disease that is one of the following:
   a) Hormone receptor-negative
   b) Hormone receptor-positive with or without endocrine therapy; OR
10. Stage IV (M1) disease activity in HER2 (ERBB2) activating mutations in combination with neratinib and fulvestrant as third-line and beyond therapy for one of the following:
   a) Hormone receptor positive HER2-negative disease in patients who have already received a CDK4/6 inhibitor therapy
   b) Triple negative disease; OR
11. Stage IV (M1) disease activity in HER2 (ERBB2) activating mutations in combination with tucatinib with or without fulvestrant as third-line and beyond therapy for one of the following:
   a) Hormone receptor positive HER2-negative disease in patients who have already received a CDK4/6 inhibitor therapy
   b) Triple negative disease; OR

Invasive Breast Cancer

For **NCCN** required criteria coverage:

12. Preoperative systemic therapy for HER2-positive tumors and locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease for one of the following:
   a) Component of TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) regimen
   b) In combination with docetaxel with or without pertuzumab following AC regimen
   c) In combination with paclitaxel, carboplatin and pertuzumab
   d) In combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   e) In combination with paclitaxel and pertuzumab following AC regimen (dose-dense or every 3 weeks)
   f) In combination with docetaxel and cyclophosphamide
   g) In combination with paclitaxel and pertuzumab
   h) In combination with docetaxel and pertuzumab

   Note: It is acceptable to change administration sequence to taxane followed by AC; OR

13. Adjuvant systemic therapy for HER2-positive pT1-3 and pN0 or pN+ tumors disease with one of the following:
   a) In combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks)
   b) In combination with docetaxel following AC regimen
   c) In combination with paclitaxel, carboplatin and pertuzumab for pT2-3 and pN0 or pN+ tumors only
   d) In combination with docetaxel and cyclophosphamide
   e) Component of TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab) regimen for pT2-3 and pN0 or pN+ tumors only
   f) In combination with pertuzumab and paclitaxel following AC regimen (dose-dense or every 3 weeks) for pT2-3 and pN0 or pN+ tumors only

g) In combination with pertuzumab and docetaxel following AC regimen for pT2-3 and pN0 or pN+ tumors only
h) In combination with paclitaxel and pertuzumab for pT2-3 and pN0 or pN+ tumors only
i) Component of TCH (docetaxel, carboplatin, and trastuzumab) regimen
j) In combination with docetaxel and pertuzumab
k) In combination with paclitaxel for low-risk T1, N0, M0, HER2-positive tumors particularly for patients not eligible for other standard adjuvant regimens due to comorbidities

Notes:
1. It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC
2. If there is no residual disease after preoperative therapy or no preoperative therapy, complete up to one year of HER2 targeted therapy with trastuzumab with or without pertuzumab after completing the planned chemotherapy regimen course. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used; OR

14. Adjuvant systemic therapy for patients with HER2-positive tumors and locally advanced disease following completion of planned chemotherapy and following mastectomy or breast-conserving surgery (BCS) with surgical axillary staging for one of the following:
    a) With or without pertuzumab if ypT0N0 or pCR
    b) With or without pertuzumab if ypT1-4N0 or ypN≥1 (if ado-trastuzumab discontinued for toxicity)
    c) With pertuzumab if ypT1-4N0 or ypN≥1 and node positive at initial staging (if ado-trastuzumab discontinued for toxicity)
    d) With pertuzumab if ypT0N0 or pCR and node positive at initial staging; OR
15. Treatment of recurrent unresectable (local or regional) or stage IV (M1) hormone receptor-positive human epidermal growth factor receptor 2 (HER2)-positive disease in postmenopausal women or premenopausal women treated with (or without if used with tamoxifen) ovarian ablation/suppression for one of the following:
    a) In combination with tamoxifen
    b) In combination with fulvestrant
    c) In combination with aromatase inhibition with or without lapatinib
    d) First-line therapy in combination with an aromatase inhibitor and pertuzumab with or without palbociclib
    e) Fourth-line therapy and beyond in combination with abemaciclib and fulvestrant

    Note: Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis; OR

16. Recurrent unresectable (local or regional) or stage IV (M1) HER2-positive disease that is either hormone receptor-negative, or hormone receptor-positive with or without endocrine therapy for one of the following:

a) First-line therapy in combination with pertuzumab with either docetaxel or paclitaxel
b) Fourth-line therapy and beyond in combination with docetaxel, vinorelbine, or capecitabine, or with paclitaxel with or without carboplatin
c) Fourth-line therapy and beyond in combination with cyclophosphamide, eribulin, gemcitabine, ixabepilone, lapatinib (without cytotoxic therapy), or albumin-bound paclitaxel
d) In combination with pertuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab; OR

17. Second or third-line therapy and beyond in combination with capecitabine and tucatinib (preferred in patients with both systemic and CNS progression in the third-line setting and beyond) for recurrent unresectable (local or regional) or stage IV (M1) HER2-positive disease that is one of the following:
    a) Hormone receptor-negative
    b) Hormone receptor-positive with or without endocrine therapy; OR
18. Stage IV (M1) disease and HER2 activity in HER2 (ERBB2) activating mutations in combination with neratinib and fulvestrant as third-line and beyond therapy for one of the following:
    a) Hormone receptor positive HER2-negative disease in patients who have already received a CDK4/6 inhibitor therapy
    b) Triple negative disease; OR
19. Stage IV (M1) disease activity in HER2 (ERBB2) activating mutations in combination with tucatinib with or without fulvestrant as third-line and beyond therapy for one of the following:
    a) Hormone receptor positive HER2-negative disease in patients who have already received a CDK4/6 inhibitor therapy
    b) Triple negative disease.[3]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD 10, and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C50	Malignant neoplasm of breast

J9356	Injection, trastuzumab, 10 mg and hyaluronidase-oysk

Revision and Review History

No.	Description	Date
1	Original Effective Date:	4/6/2026
2	Policy Annual Review Dates:	
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	4/30/26
5	Revision Changes	

References

[1] How Herceptin is thought to work. Genetech. https://www.herceptin.com/hcp/adjuvant-breast-cancer/about-herceptin/how-herceptin-is-thought-to-work.html. Accessed April 6, 2026.

[2] Herceptin Hylecta (Trastuzumab and hyaluronidase-oysk) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761106s010lbl.pdf. Accessed April 6, 2026.

[3] National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed January 15, 2026.

[4] What we do. U.S. Food & Drug Administration. https://www.fda.gov/about-fda/what-we-do. Accessed April 6, 2026.

[5] Cheng X. A Comprehensive Review of HER2 in Cancer Biology and Therapeutics. Genes (Basel). 2024;15(7):903. Published 2024 Jul 11. https://pubmed.ncbi.nlm.nih.gov/39062682/. Accessed April 6, 2026.

[6] National Comprehensive Cancer Network. https://www.nccn.org/home. Accessed April 6, 2026.