These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.

Trastuzumab and Hyluronidase-oysk (Herceptin Hylecta) Clinical Guideline for Outpatient Subcutaneous Administration

Section: Clinical Guideline
Policy ID: CG039
Effective: 10/20/2022
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Approved by, Title and Date Approved: Kathleen Patrick, President, 10/20/22, 9/8/25

I. BACKGROUND

Trastuzumab and hyaluronidase-oysk is a subcutaneous combination product for the treatment of HER2-overexpressing breast cancer. It is composed of trastuzumab, a HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase. Trastuzumab inhibits proliferation of tumor cells that overexpress the HER2 proto-oncogene. Hyaluronidase is the enzyme responsible for breaking down hyaluronan in the extracellular matrix of extracellular tissue. By depolymerizing hyaluronan, hyaluronidase increases subcutaneous permeability; therefore, allowing increased systemic absorption of trastuzumab. It is indicated as an adjuvant therapy in combination with breast cancer regimens or as a single agent following multi-modal, anthracycline-based therapy. It is similarly used in the treatment of metastatic breast cancer. The following outlines the procedures for servicing patients in need of outpatient Trastuzumab and hyaluronidase-oysk home injections.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon dispensing pharmacy's admission criteria.

B. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:
   1. Prescriber preference
   2. Allergy profile
   3. Age
   4. Ability to secure contracted nursing for subsequent injections
   5. Other relevant social and/or medical history

C. Physician orders must include:
   1. Drug
   2. Dose
   3. Route of administration
   4. Frequency of administration
   5. Emergency medications per protocol
   6. Orders for pre-medications, if applicable
   7. Routine lab monitoring, if applicable

D. Baseline lab tests prior to therapy
    1. Pregnancy tests are recommended for female patients of childbearing age.
    2. Baseline cardiac function

E. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless a more comprehensive patient-specific orders are provided by the physician. See Appendix B (Nursing CarepathRx policy on *Management of Allergic/Anaphylactic Reactions*)

III. PHARMACOLOGIC OVERVIEW

Refer to manufacturer's full Prescribing Information for most up to date information

A. Indications: Adjuvant treatment, HER2 positive breast cancer, neoadjuvant HER2 positive breast cancer, metastatic HER2 positive breast cancer, Metastatic relapsed or refractory HER2 positive breast cancer (with or without brain metastases)

B. Dosing:
    1. Trastuzumab 600 mg/hyaluronidase 10,000 units subcutaneously every three weeks

C. Dose adjustments

    1. There are no dosage adjustments for renal or hepatic failure provided in the manufacturer's labeling
    2. Adjustments based on Left Ventricular Ejection Fraction:
        a. Withhold Trastuzumab and hyaluronidase-oysk for ≥16% absolute decrease in left ventricular ejection fraction (LVEF) from pre-treatment values or LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values.
        b. Trastuzumab and hyaluronidase-oysk may be resumed if, within 4−8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.
        c. Permanently discontinue Trastuzumab and hyaluronidase-oysk for a persistent (>8 weeks) LVEF decline or for suspension of Trastuzumab and hyaluronidase-oysk dosing on more than 3 occasions for cardiomyopathy.
    3. If a dose is missed, administer it as soon as possible. Ensure that the interval between subsequent doses is at least three weeks.

D. Duration:
    1. Adjuvant breast cancer: 52 weeks, or until disease recurrence, unless otherwise specified by ordering provider. (not recommended for use beyond 1 year)
    2. Neoadjuvant breast cancer: every 3 weeks for 10 cycles, unless otherwise specified by ordering provider.
    3. Metastatic breast cancer: Until progression of disease.

E. Contraindications: None

F. Precautions
    1. Cardiomyopathy: Trastuzumab and hyaluronidase-oysk can cause left ventricular cardiac dysfunction, including arrhythmias, hypertension, symptomatic decline in LVEF, and cardiac failure. Assess left ventricular ejection fraction (LVEF) prior to initiation of trastuzumab and hyaluronidase-oysk and then every 3 months during therapy. Repeat at 4-week intervals if trastuzumab and hyaluronidase-oysk is withheld for significant LVEF decline. LVEF measurements should be taken every 6

months for at least 2 years following completion of therapy with Trastuzumab and hyaluronidase-oysk

2. Embryo-Fetal Toxicity: Fetal harm (pulmonary hypoplasia, skeletal abnormalities, neonatal death) is associated when administered in pregnant women. Verify pregnancy status of female patients for initiation of treatment. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Trastuzumab and hyaluronidase-oysk.

3. Lactation: There is no information regarding the presence of trastuzumab and hyaluronidase-oysk in human milk, the effects on the breast-fed infant, or the effects on milk production.

4. Immunogenicity: There is a potential for immunogenicity. Detection of antibody formation depends on the sensitivity and specificity of the assay and is influenced by multiple factors. In the HannaH study, the incidence of anti-trastuzumab antibodies was 10% in patients receiving IV trastuzumab and 16% in those receiving trastuzumab and hyaluronidase-oysk. The incidence of anti-recombinant human hyaluronidase antibodies was 21% in the trastuzumab and hyaluronidase-oysk arm; however, none of the patients tested positive for neutralizing antibodies.

5. Pulmonary Toxicity: Fatal pulmonary toxicity may result. Other toxicities include dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, pulmonary insufficiency, and hypoxia. Consider baseline pulmonary function and concomitant disease states prior to treatment. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

6. Exacerbation of Chemotherapy-Induced Neutropenia: Randomized controlled trials have shown increased risk of febrile neutropenia in patients receiving trastuzumab and chemotherapy compared with chemotherapy alone. The incidence of septic death was comparable between patients who received trastuzumab and those who did not.

7. Hypersensitivity: Severe administration-related reactions, including hypersensitivity and anaphylaxis have occurred. Monitor patients for these reactions, especially during the first administration, and discontinue therapy in patients who experience severe reactions. For patients experiencing reversible Grade 1 or 2 hypersensitivity reactions, consider pre-medication with an analgesic, antipyretic, or an antihistamine prior to re-administration of trastuzumab and hyaluronidase-oysk.

G. Pharmacokinetics

PK parameters of Trastuzumab following Subcutaneous Administration of HERCEPTIN HYLECTA*

Absorption	
Absolute Bioavailability	0.77 (13)
First-order absorption rate, ka (day^{-1})	0.4 (2.92)†
T_{max} (day)	3 (1-14)‡
Distribution	
Volume of Central Compartment (L)	2.9 (19.1)
Elimination	
Linear Elimination Clearance (L/day)	0.11 (30)
Non-linear Elimination V_{max} (mg/day)	11.9 (19.9)†
Non-linear Elimination K_m (mg/L)	33.9 (38.6)†

* Parameters represented as geometric mean (%CV) unless otherwise specified
† Residual standard error
‡ Median (range)

H. Adverse Reactions

1. Cardiovascular: Hypertension (2% to 8%), cardiac arrhythmia (5%), reduced ejection fraction (5%), left ventricular dysfunction (3%), palpitations (2%), tachycardia (2%), cardiac failure (1%), edema (12% to 14%), flushing (12% to 14%)
2. Dermatologic: Alopecia (9% to 63%), Injection site disorder (10% to 20%), Nail changes (10% to 14%), Rash (17% to 26%), Erythema at injection site (7%), pain at injection site (6%)
3. Gastrointestinal: Nausea (15%- 49%), diarrhea (21%-34%), vomiting (7% - 23%), stomatitis (8%-21%), decreased appetite (20%), constipation (9%-14%), dysgeusia (10%)
4. Hematologic & oncologic: Neutropenia (6% to 44%; grade ≥3: 4% to 30%), anemia (8% to 12%; grade ≥3: <1%), leukopenia (1% to 11%; grade ≥3: 1% to 5%)
5. Immunologic: Anaphylaxis, antibody development
6. Infections: Urinary tract infection (6% to 4%), viral infection (5%)
7. Neurologic: Arthralgia (18% to 21%), myalgia (17% to 21%), dizziness (6% to 10%), pain (5% to 8%), insomnia (7%), paresthesia (6%)
8. Musculoskeletal: Asthenia (12% to 25%), headache (13% to 17%) sensory neuropathy (14%-20%),
9. Respiratory: Upper respiratory tract infection (19% to 24%), cough (11% to 12%), dyspnea (7% to 8%)
10. Miscellaneous: Fatigue (33% to 46%), inflammatory disease of mucous membrane (6% to 10%), radiation injury (skin: 14%), fever (11% to 13%)

I. Drug Interactions: If possible, avoid anthracycline-based therapy for up to 7 months after stopping Trastuzumab and hyaluronidase-oysk. If anthracyclines are used, closely monitor the patient's cardiac function. Additional drug-drug interactions may exist. Live vaccines should not be administered to patients receiving immunosuppressive therapy. Consult interaction database for patient specific assessment.

IV. ADMINISTRATIVE GUIDELINES

A. Subcutaneous Trastuzumab and hyaluronidase-oysk should be administered by a healthcare professional

1. The injection site should be alternated between the left and right thighs, delivered at least 2.5 cm from the previous site, and into healthy, unmarked skin.

2. Other subcutaneous medications should be injected at different sites.
3. Do not split the dose between 2 syringes or 2 sites of administration

B. Compatibility: Drug solution is compatible with polypropylene and polycarbonate syringe materials, as well as stainless steel transfer and injection needles.

C. **Hazardous handling: It is the responsibility of the dispensing pharmacy to ensure medication handling follows organizational policies and procedures. This medication meets the definitions of a hazardous drug as outlined by the National Institute for Occupational Safety and Health (NIOSH). Consider the use of closed system transfer devices (CSTD) if applicable.**

V. NURSING PROCEDURE

A. Supplies - If following NIOSH and USP <800> recommendations for handling, administration, and disposal, supplies may include but are to limited to:

1. Alcohol Swabs
2. Gloves
3. Tape
4. Transfer needle
5. Hypodermic needle (25G-27G)
6. Appropriately sized syringes with needles
7. Chemo spill kit and hazardous drug spill procedure
8. Chemotherapy gloves, as needed
9. Protective gown
10. Chemotherapy prep mat, as needed
11. Trace/chemo disposable mail back container

B. Prescription items:

1. Vial of Trastuzumab and hyaluronidase-oysk
2. Epinephrine kit per protocol

C. How Supplied:

1. Trastuzumab and hyaluronidase-oysk injection for subcutaneous use supplied as a sterile, preservative-free, colorless to yellowish, clear to opalescent solution Trastuzumab and hyaluronidase-oysk 600 mg/10,000 units in 5mL in a single-dose vial.

D. Storage and Handling:

1. Store Trastuzumab and hyaluronidase-oysk vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

E. Procedures:

1. Explain the reason for the visit and use of Trastuzumab and hyaluronidase-oysk.
2. Don chemo gloves and gown. Prepare chemotherapy prep mat.

3. Counsel patient on warnings, precautions, and potential side effects including but not limited to hypersensitivity, infusions related reactions, pulmonary toxicity, cardiomyopathy, and neutropenia.

4. Prepare product:

    a. The medication should be visually inspected for particulate matter and discoloration prior to use.

        1) The solution is available in a single use vial as a solution ready for injection (no dilution necessary).
        2) Draw up 5 mL using the supplied syringe and transfer needle.
        3) Immediately prior to administration, attach the hypodermic injection needle to the syringe for injection. Do not attach until time of administration to avoid clogging.

5. The injection site should be alternated between the left and right thigh only, delivered at least 1 inch from the previous site, and into healthy, unmarked skin.

    a. To minimize discomfort:
        1) Slow injection will promote effects of hyaluronidase
        2) Inject at a 90-degree angle; if the syringe is at a 45-degree angle, ensure the bevel is pointed upward

6. Infusion Rates: Slowly inject the trastuzumab and hyaluronidase-oysk over 2-5 minutes into the subcutaneous tissue.
7. Discard waste in chemotherapy/trace disposable container.
8. Post infusion monitoring: Monitor patient and vital signs periodically during the infusion and 30 minutes after the infusion is complete per CarePathRx Nursing Best Practice Administration Guidelines.

VI. CLINICAL MONITORING

A. Prior to therapy

1. Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

    a. Baseline LVEF measurement prior to initiation of Trastuzumab and hyaluronidase-oysk.
    b. Pregnancy status

        1) Verify the pregnancy status of females of reproductive potential prior to the initiation. Exposure within 7 months prior to conception may result in fetal harm. Effective contraception should be used during treatment and for at least 7 months after the last dose.

B. During therapy

1. Cardiac monitoring: LVEF monitoring at specified time intervals
2. Monitor closely for signs/symptoms of hypersensitivity (particularly during the first dose)
3. Monitor closely for pulmonary toxicity (dyspnea, non-cardiogenic pulmonary edema, hypoxia)

4. Patients should be aware of the signs and symptoms of cardiomyopathy symptoms that necessitate contacting their physician (weight gain >5 pounds in 24 hours, dizziness, loss of consciousness).

Please refer to the package insert for the most up to date guidance on this medication.

REFERENCES

HERCEPTIN HYLECTA (trastuzumab and hyaluronidase-oysk). South San Francisco CA; Genentech, Inc. 2019

Trastuzumab/hyaluronidase-oysk. In-Depth Answers. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2022. Accessed June 25 , 2025. https://www.micromedexsolutions.com

Trastuzumab/hyaluronidase-oysk. UpToDate, Connor RF (Ed), Wolters Kluwer. Accessed on June 25, 2025.https://www.uptodate.com.

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APPENDIX B: EPINEPRINE KIT INSTRUCTIONS FOR IM INJECTION

Emergency Medication After Your Infusion

Please call 1-800-755-4704 if you have any questions or concerns. We are available 24 hours a day, 7 days a week. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.

Start with a clean work surface and clean hands.

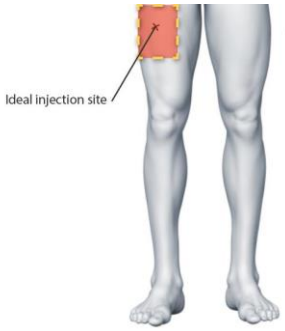
Open the supply bag labeled Epinephrine Kit Contents.

1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

2. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
3. Using an **alcohol swab, wipe the neck of the epinephrine ampule**
4. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
5. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**
6. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdrawal all the medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
7. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
8. **Push the air out of the syringe by gently pushing on the plunger**.
9. Replace the cap on the brown filter needle.
10. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



2. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
3. **Push the needle into your leg muscle straight** in at a 90-degree angle.
4. **Inject the medication** by depressing the plunger in a slow and steady motion.
5. **Remove the needle** and wipe the site with the alcohol wipe.

Place all trash in the bag and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.

Call 911 or have someone drive you to the emergency department.