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.

# Pertuzumab/Traztuzumab/Hyaluronidase-zzxf (Phesgo) Clinical Guideline for Home Intravenous Therapy

**Section:** Clinical Guideline
**Policy ID:** CG038
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**Approved by, Title and Date Approved:** Kathleen Patrick, President 10/26/22, 9/8/25

## I. BACKGROUND

Phesgo (pertuzumab/trastuzumab/hyaluronidase-zzxf) is a subcutaneous combination product used with chemotherapy adjuvant and neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. It is also used in combination with docetaxel for treatment of patients with HER2 positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy.

Phesgo is composed of pertuzumab and trastuzumab, both HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase. Trastuzumab inhibits proliferation of tumor cells that overexpress the HER2 proto-oncogene. Pertuzumab binds a different HER2 epitope than trastuzumab, inhibiting dimerization and downstream signaling in HER2-overexpressing tumor cells. Hyaluronidase is the enzyme responsible for breaking down hyaluronan in the extracellular matrix of extracellular tissue. It increases subcutaneous permeability; therefore, allowing increased systemic absorption of trastuzumab. The following outlines the procedures for servicing patients in need of outpatient pertuzumab/trastuzumab/hyaluronidase-zzxf 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 contacted 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
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 evaluation

E. Dispensing pharmacy treatment protocol for hypersensitivity or anaphylaxis reactions with IM epinephrine will be instituted unless a more comprehensive patient-specific orders are provided by 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: in combination with chemotherapy for:

    1. Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node positive)
    2. Adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence
    3. HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

B. Dosing:

    1. Loading dose: 1200mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase once.
    2. Maintenance dose: 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase every three weeks.

C. Dose adjustments:

    1. There are no dosage adjustments for renal or hepatic failure provided in the manufacturer's labeling

    2. Delayed or Missed dosing:
        a. If the time between two sequential injections is less than 6 weeks, administer the maintenance dose of 600 mg, 600 mg, and 20,000 units/10 mL Do not wait until the next planned dose.
        b. If the time between two sequential injections is 6 weeks or more, re-administer the initial dose of 1,200 mg, 600 mg, and 30,000 units/15 mL, followed every 3 weeks thereafter by a maintenance dose of 600 mg, 600 mg, and 20,000 units/10 mL.

3. Dose Adjustments based on Left Ventricular Ejection Fraction: Assess left ventricular ejection fraction (LVEF) prior to initiation at regular intervals during treatment as indicated in table below.

<table>
<tr><th></th><th>Pre-treatment LVEF:</th><th>Monitor LVEF every:</th><th colspan="2">Withhold PHESGO for at least 3 weeks for an LVEF decrease to:</th><th colspan="2">Resume PHESGO after 3 weeks if LVEF has recovered to:</th></tr>
<tr><td rowspan="2">Early Breast Cancer</td><td rowspan="2">≥ 55%*</td><td rowspan="2">~12 weeks (once during neoadjuvant therapy)</td><td colspan="2" rowspan="2"><50% with a fall of ≥10%-points below pre-treatment value</td><td colspan="2">Either</td></tr>
<tr><td>≥50%</td><td><10% points below pre-treatment value</td></tr>
<tr><td rowspan="2">Metastatic Breast Cancer</td><td rowspan="2">≥ 50%</td><td rowspan="2">~12 weeks</td><td colspan="2">Either</td><td colspan="2">Either</td></tr>
<tr><td><40%</td><td>40%-45% with a fall of ≥10%-points below pre-treatment value</td><td>>45%</td><td>40%-45% with a fall of <10%-points below pre-treatment value</td></tr>
</table>

* For patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting PHESGO

4. If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, has declined further, and/or the patient is symptomatic, permanently discontinue pertuzumab trastuzumab and hyaluronidase.

D. Duration:

1. Neoadjuvant: every 3 weeks with chemotherapy preoperatively for 3 to 6 cycles.
2. Adjuvant: every 3 weeks with chemotherapy postoperatively for a total of 1 year (up to 18 cycles).
3. Metastatic Breast Cancer (MBC): every 3 weeks until progression of disease

E. Contraindications:

1. Pertuzumab/trastuzumab/hyaluronidase-zzxf is contraindicated in patients with known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or any of its excipients.

F. Precautions:

1. Cardiomyopathy: Pertuzumab/trastuzumab/hyaluronidase-zzxf administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving pertuzumab/trastuzumab/hyaluronidase-zzxf with anthracycline containing chemotherapy regimens. Avoid anthracycline-based therapy for up to 7 months after stopping pertuzumab/trastuzumab/hyaluronidase-zzxf. If anthracyclines are used, carefully monitor cardiac function.
    a. Evaluate cardiac function prior to and during treatment with pertuzumab/trastuzumab/hyaluronidase-zzxf. Discontinue treatment in patients receiving adjuvant therapy and withhold treatment in patients with metastatic disease for clinically significant decrease in left ventricular function

2. Embryo-Fetal Toxicity: Fetal harm (pulmonary hypoplasia, skeletal abnormalities,

and neonatal death) is associated when administered in pregnant women. Verify pregnancy status of female patients for initiation of treatment. Advise patients of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of pertuzumab/trastuzumab/hyaluronidase-zzxf. There is no information regarding the presence of pertuzumab, trastuzumab or hyaluronidase in human milk, the effects on the breastfed infant, or the effects on milk production

3. Lactation: There is no information regarding the presence of pertuzumab, trastuzumab or hyaluronidase in human milk, the effects on the breast-fed infant, or the effects on milk production.
4. 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.
5. 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 FeDeriCa trial, the incidence of anti-pertuzumab antibodies was 12.9% and 2.1% for anti-trastuzumab antibodies; incidence of neutralizing antibodies (NAb) to pertuzumab and to trastuzumab was 6% (2/31) and 20% (1/5); However, no identified clinically significant effect of anti-pertuzumab and anti-trastuzumab antibodies on the safety. The effect of antibodies on the pharmacokinetics and effectiveness of pertuzumab/trastuzumab/hyaluronidase-zzxf is unknown.
6. Exacerbation of Chemotherapy-Induced Neutropenia: a randomized controlled trial has shown increased risk of febrile neutropenia in patients receiving trastuzumab and chemotherapy compared with chemotherapy alone.
7. Hypersensitivity: Severe administration-related reactions, including hypersensitivity and anaphylaxis have occurred. Monitor patients for these reactions for 15-30 minutes after each administration. 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 pertuzumab/trastuzumab/hyaluronidase-zzxf.

G. Pharmacokinetics

**PK Parameters of Pertuzumab and Trastuzumab Following Subcutaneous Administration of PHESGO ***

| | Pertuzumab[a] | Trastuzumab[b] |
|---|---|---|
| **Absorption** | | |
| Absolute Bioavailability | 0.7 (18) | 0.8 (13) |
| First-order absorption rate, ka ($day^{-1}$) | 0.4 (8) † | 0.4 (2.9) † |
| $T_{max}$ (day) | 4 (1 – 21) ‡ | 4 (1– 22) ‡ |
| **Distribution** | | |
| Volume of Central Compartment (L) | 2.8 (35) | 2.9 (19) |
| **Elimination** | | |
| Linear Elimination Clearance (L/day) | 0.2 (24) | 0.1 (30) |
| Non-linear Elimination $V_{max}$ (mg/day) | N/A | 12 (20) |
| Non-linear Elimination $K_m$ (mg/L) | N/A | 34 (39) |

H. Adverse Reactions

1. Dermatologic: Alopecia (77%), skin rash (16%), xeroderma (15%), injection-site reaction (13% to 15%) pain at injection site (2%), radiation injury (skin: 19% to 20%), Dermatitis (7%), erythema of skin (9%), nail discoloration (9%), nail disease (7%), palmar-plantar erythrodysesthesia (6%), paronychia (7%), pruritus (3% to 10%)
2. Endocrine & metabolic: Decreased serum albumin (16%), decreased serum sodium (13%), hot flash (11% to 12%), hyperkalemia (13%), weight loss (11%), Decreased serum glucose (9%), hypokalemia (7%), increased serum sodium (7%)
3. Gastrointestinal: Constipation (22%), decreased appetite (17%), diarrhea (17% to 60%; grades 3/4: 7%), dysgeusia (17%), dyspepsia (12% to 14%), nausea (60%; grades 3/4: 2%), stomatitis (15% to 25%; grades 3/4: ≤1%), vomiting (20%; grades 3/4: <1%)
4. Hematologic & oncologic: Anemia (36%; grades 3/4: 2%), decreased absolute lymphocyte count (89%; grades 3/4: 37%), decreased platelet count (27%), neutropenia (22%; grades 3/4: 14%)
5. Hepatic: Increased serum alanine aminotransferase (58%), increased serum aspartate aminotransferase (50%)
6. Nervous system: Asthenia (11% to 31%), dizziness (13%), fatigue (29%), headache (17%), insomnia (17%), peripheral neuropathy (12%; grades 3/4: <1%), peripheral sensory neuropathy (16%), procedural pain (13%), fever (13%)
7. Neuromuscular & skeletal: Arthralgia (19% to 24%), myalgia (25%)
8. Renal: Increased serum creatinine (84%)

I. Drug Interactions: If possible, avoid anthracycline-based therapy for up to 7 months after stopping pertuzumab and trastuzumab. If anthracyclines are used, carefully monitor the patient's cardiac function. Drug-drug interactions may exist. Consult interaction database for patient specific assessment.

## IV. ADMINISTRATIVE GUIDELINES

A. Subcutaneous Pertuzumab, trastuzumab, and hyaluronidase 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. If administering with docetaxel or paclitaxel, taxane should be given AFTER pertuzumab/trastuzumab/hyaluronidase-zzxf administration

C. Compatibility: Drug solution is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, PVC, and fluorinated ethylene polypropylene.

D. 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 GUIDELINES

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 Pertuzumab, 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 pertuzumab/trastuzumab/hyaluronidase-zzxf 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 reason for the visit and pertuzumab/trastuzumab/hyaluronidase-zzxf**.**
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.
    a. Prepare product:
        1) The medication should be visually inspected for particulate matter and discoloration prior to use.
            a) The solution is available in a single use vial as a solution ready for injection (no dilution necessary).
        2) Draw up 15 mL (initial dose) or 10 mL (maintenance dose) 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.
    b. The injection site should be alternated between the left and right thighs only, delivered at least 1 inch from the previous site, and into healthy, unmarked skin.

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

4. Infusion Rates: The initial dose should be administered over 8 minutes for loading dose and 5 minutes for maintenance dose. Inject slowly into the subcutaneous tissue at a rate of approximately 2 ml per minute.
5. 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. Baseline cardiac monitoring.
2. Pregnancy status
   a. Verify the pregnancy status of females of reproductive potential prior to the initiation.
   b. 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 that necessitate contacting their physician (dizziness, angioedema, breathing problems, or chest pain).
3. Monitor closely for pulmonary toxicity (dyspnea, non-cardiogenic pulmonary edema, hypoxia)
4. Patients should be aware of the signs and symptoms of cardiomyopathy and symptoms that necessitate contacting their physician (weight gain >5 pounds in 24 hours, dizziness, loss of consciousness, swelling of the face).

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

## REFERENCES


1. PHESGO Prescribing Information. South San Francisco CA; Genentech, Inc. 2020
2. PHESGO Dosing and Administration Guide. South San Francisco CA; Genentech, Inc. 2021. Accessed July 9, 2025.
3. PHESGO. UpToDate. Accessed July 9, 2025.
4. United States Pharmacopeia (USP). General Chapter, <797> Pharmaceutical Compounding—Sterile Preparations. (2023) USP-NF. Rockville, MD: United States Pharmacopeia. Accessed April 1, 2025

# APPENDIX B: EPINEPRINE KIT INSTRUCTIONS FOR IM INJECTION

## Emergency Medication After Your Infusion

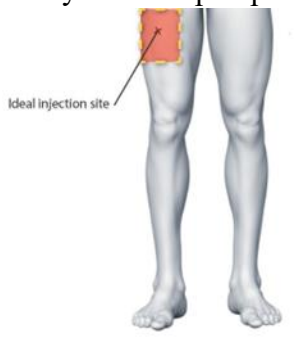
**Please call 1-800-755-4704 if you have any questions or concerns. We are available 24 hours a day, 7 days a week. In the event of an emergency, always call 911.**
**Your nurse will tell you when you need to use Emergency Medications.**
Start with a clean work surface and clean hands.
**Open the supply 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.