CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

CLINICAL GUIDELINES FOR OUTPATIENT SUBCUTANEOUS ADMINISTRATION OF PERTUZUMAB/TRAZTUZUMAB/HYALURONIDASE-ZZXF (PHESGO)

Section: Nursing
Compliance: ACHC Infusion Pharmacy
ACHC Standards: N/A
URAC Standards: N/A
TJC Standards: N/A
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Reviewed:
Revised:
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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. 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 ≥18 years
   4. Ability to secure nursing for subsequent injections
   5. Other relevant social and/or medical history

C. Physician orders must include:
    1. Drug and dose
    2. Route of administration
    3. Frequency of administration
    4. Emergency medications per protocol
    5. Orders for pre-medications

D. 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.

E. Pregnancy status

F. Assessment of left ventricular ejection fraction (LVEF)

G. Baseline cardiac evaluation

H. Hepatitis B virus screening with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), total Ig or IgG, and antibody to hepatitis B surface antigen (anti-HBs) prior to beginning systemic anticancer therapy

I. Dispensing pharmacy treatment protocol for IM epinephrine will be instituted unless more comprehensive patient-specific orders are provided by physician.

III. PHARMACOLOGY OVERVIEW

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

A. Indications and Dosing
    1. Loading dose: 1200mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase
    2. Maintenance dose: 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase

B. 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

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
        b. Do not wait until the next planned dose

c. If the time between two sequential injections is 6 weeks or more, re-administer the initial loading dose followed every 3 weeks thereafter by a maintenance dose

3. Dose Adjustments based on Left Ventricular Ejection Fraction
    a. 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

<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

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

E. Precautions
    1. **Cardiomyopathy**
        a. 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.
        b. 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**
        a. 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. **Pulmonary Toxicity**
    a. 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
4. **Exacerbation of Chemotherapy-Induced Neutropenia**
    a. Randomized controlled trial have shown increased risk of febrile neutropenia in patients receiving trastuzumab and chemotherapy compared with chemotherapy alone
5. **Hypersensitivity**
    a. 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

F. Adverse Reactions
1. Neoadjuvant and Adjuvant Treatment of Breast Cancer (>30%): alopecia, nausea, diarrhea, anemia, and asthenia
2. Metastatic Breast Cancer (> 30%): diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy.
3. Hypersensitivity and administration-related reactions, injection site reactions, and injection site pain

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. Drug Interactions
    1. No formal drug interaction studied have been performed. Clinically significant interactions among pertuzumab, trastuzumab, and concomitant medications used in clinical trials have not been observed.
    2. **Anesthetics**
        a. Benzocaine, bupivacaine, butacaine, chloroprocaine, dibucaine, etidocaine, lidocaine, mepivacaine, prilocaine, procaine, proparacaine, propoxycaine, ropivacaine, tetracaine
            i. The hyaluronidase component can increase incidences of systemic reactions to anesthetics via increased diffusion.
    3. **Anthracyclines**
        a. Daunorubicin, doxorubicin, epirubicin, idarubicin, pirarubicin, valrubicin. Increased risk of cardiac dysfunction; avoid anthracycline-based therapy for up to 7 months after stopping pertuzumab/trastuzumab/hyaluronidase-zzxf. If anthracyclines are used, carefully monitor cardiac function.
    4. **Phenylephrine (Systemic)**
        a. Hyaluronidase may enhance the vasoconstricting effect of phenylephrine.

IV. ADMINISTRATIVE GUIDELINES

A. Recommended Handling
    1. This medication may meet the definitions of a hazardous drug as outlined by NIOSH. **It is the responsibility of the dispensing pharmacy to ensure medication handling follows organizational policies and procedures.**

B. How Supplied
    1. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection is a sterile, preservative-free, clear to opalescent, and colorless to slightly brownish solution in single-dose vials:
        i. 1,200mg pertuzumab, 600mg trastuzumab, and 30,000 units hyaluronidase/15mL (80mg, 40mg, and 2,000 units/mL)
        ii. 600mg pertuzumab, 600mg trastuzumab, and 20,000 units hyaluronidase/10mL (60mg, 60mg, 2,000 units/mL)

C. 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.
    2. Do not freeze. Do not shake.

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

E. If following NIOSH and USP <800> recommendations for handling and preparation:

1. Prepare the dose in a syringe under aseptic conditions in a containment primary engineering control
2. Withdraw prescribed dose and volume from vial into syringe
3. Label and package per pharmacy protocol
4. Syringe may be stored for up to 24 hours refrigerated followed by 4 hours at room temperature
5. Protect the medication from light, do not shake or freeze.

V. NURSING GUIDELINES

A. Supplies
   1. If following NIOSH and USP <800> recommendations for handling, administration, and disposal, supplies may include:
      a. Alcohol swabs
      b. Chemo gloves/prep pad/gown
      c. Chemo spill kit
      d. Hypodermic needle
      e. Chemo waste bin
      f. Syringe containing pertuzumab/trastuzumab/hyaluronidase-zzxf

B. Procedures
   1. Explain reason for visit and pertuzumab/trastuzumab/hyaluronidase-zzxf**. Dose must be administered by a healthcare professional.**
   2. Don appropriate PPE
   3. Remove syringe from refrigerated storage, if applicable. Solution should be administered at room temperature
   4. The medication should be visually inspected for particulate matter and discoloration prior to use.
   5. Check to ensure the correct dose is being administered: initial dose (15mL) or maintenance dose (10mL)
   6. Immediately prior to administration, attach the hypodermic injection needle to the syringe for injection. Do not attach until time of administration to avoid clogging
   7. 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.
   8. The dose should be administered over 8 minutes for loading dose and 5 minutes for maintenance dose (no more than 2 mL/min). 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
   9. Other subcutaneous medications should be injected at different sites.
   10. If administering with docetaxel or paclitaxel, taxane should be given AFTER pertuzumab/trastuzumab/hyaluronidase-zzxf administration
   11. Observe patient for a minimum of 30 minutes after dose.

Additional administration tips: Refer to manufacturer guide for most up-to-date information:

1. Do not split the dose between 2 syringes or 2 sites of administration
2. Consider asking the patient to wear loose clothing to facilitate access to the thigh area (i.e., skirt or loose shorts)
3. Ask the patient to sit back in a reclining chair or bed
4. Arrange your chair at the right level so your feet are flat on the floor, and you are able to sit up straight without twisting, bending, or reaching to administer the injection. You will be in position for at least 5 minutes.

VI. ASSESSMENT AND CLINICAL MONITORING

A. Cardiac Monitoring
   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 immediately prior to initiation of pertuzumab/trastuzumab/hyaluronidase-zzxf
      b. LVEF measurements every 3 months during and upon completion of pertuzumab/trastuzumab/hyaluronidase-zzxf
      c. Repeat LVEF measurement at 3-week intervals if pertuzumab/trastuzumab/hyaluronidase-zzxf is withheld for significant left ventricular cardiac dysfunction
      d. LVEF measurements every 6 months for at least 2 years after completion of pertuzumab/trastuzumab/hyaluronidase-zzxf

B. Monitor closely for signs/symptoms of hypersensitivity (particularly during the first dose) and/or pulmonary toxicity for at least 30 minutes following dose.

C. Patients should be aware of the signs and symptoms of a hypersensitivity reaction 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

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 September 16, 2022.

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