Pertuzumab-Trastuzumab-Hyaluronidase-zzxf (PHESGO) Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action	PHESGO is a combination product that contains pertuzumab and trastuzumab along with hyaluronidase, an endoglycosidase, for subcutaneous dispersion.
Indication(s) under Review	Use in combination with chemotherapy as: • Neoadjuvant therapy for HER2+, locally advanced, inflammatory or early stage breast cancer (EBC) as part of a treatment regimen for early breast cancer • Adjuvant therapy in HER2+ EBC at high risk of recurrence • With docetaxel for HER2+ metastatic breast cancer (MBC) who have not received prior HER2-directed therapy or chemotherapy for metastatic disease
Dosage Form(s) under Review	Injection: 1200 mg pertuzumab, 600 mg trastuzumab, 30,000 units hyaluronidase/15ml SDV 600 mg pertuzumab, 600 mg trastuzumab, 20,000 units hyaluronidase/10ml SDV

Clinical Evidence/Safety Summary

Table 1: Efficacy results from clinical trials

Study	Design	Intervention	Results
Tan, et al. FeDeriCa Inclusion: Age ≥ 18 yo; ECOG PS 0-1; HER2+, LA or inflammatory (operable) stage II-IIIC breast cancer; LVEF ≥ 55%	Randomised, open-label, multicenter, non-inferiority, phase 3 trial	One of two standard chemotherapy regimens[b] were selected prior to randomization. 4 cycles given q3 wks with NACT; post-surgery, add'l 14 cycles to 18 cycles total IV P 840mg LD x1, then 420mg MD T 8mg/kg LD x1, then 6mg/kg MD SC P 1200mg-T 600mg LD x1, then P 600mg- T 600mg MD	IV group N=252; SubQ group N=248 Primary endpoint non-inferiority[a] of C#7 C_{trough} of fixed-dose vs. IV pertuzumab GMR 1.22 (90% CI 1.14-1.31) [above the pre-specified 0.8 noninferiority margin] Secondary endpoint non-inferiority[a] of C#7 C_{trough} of fixed-dose vs. IV trastuzumab GMR 1.33 (90% CI 1.24-1.43) [above the pre-specified 0.8 noninferiority margin] Trough values pre-C#8 were selected as steady-state conc should be reached and was matched to total pathologic CR Total path CR 59.7 vs. 59.7% (IV vs. Fixed) Clinical RR 85 vs. 83% (IV vs. Fixed)

O'Shaughnessy, et al. PHranceSCa Inclusion: Age ≥ 18 yrs, HER2+ (IHC 3+ and/or ISH+), inflammatory, locally advanced or EBC and completed NACT, P, T and surgery; ECOG PS 0-1, LVEF ≥ 55%	Randomized, open-label, international, multi-center, crossover P2 study 39 sites in 16 countries	s/p surgery, patients were randomized 1:1 to either 3 cycles IV P + T, then 3 cycles SC P + T, or vice versa, then each patient selected SC or IV to complete up to 18 cycles Assessments completed via patient preference questionnaire (PPQ); Health care professional questionnaire (HCPQ)	N= 160 patients randomized Primary endpoint Evaluate patient preference for SC P + T 136 (85%) preferred SC; 22 (13.8%) preferred IV 2 (1.4%) no preference Main reasons for SC preference: Reduced clinic time Comfort during administration Main reasons for IV preference: More comfortable during administration Lower level of injection site pain Median drug preparation time was less for SC vs. IV (5 min vs. 15-20 min); Median administration time was less for SC vs. IV (33-50 min vs. 130-300 min) Most AEs were grade 1-2; Rates of AEs before/after switches: C#1-3 IV 78% -> SC 73% C#1-3 SC 78% -> IV 64% Limitation: small numbers of patients; methods for HCP to determine prep time, clinic time were not described

[a]noninferior if lower bound of 90% CI of the geometric mean ratio (GMR) ≥ 0.8
[b]Chemotherapy options: 4 cycles ddAC-> paclitaxel or 4 cycles AC -> docetaxel; NACT neoadjuvant chemotherapy

Boxed warnings	Cardiomyopathy. May result in cardiac failure manifest as CHF and decreased LVEF; greatest risk with concurrent anthracycline therapy Embryo-fetal-toxicity. May result in birth defects and death Pulmonary toxicity. May result in serious and/or fatal pulmonary toxicity
Contraindications	Patients with known hypersensitivity to pertuzumab, trastuzumab, hyaluronidase or any excipients
Warnings/Precautions	Cardiomyopathy. May cause hypertension, arrhythmias, LV dysfunction, heart failure, cardiomyopathy and asymptomatic LVEF decline. Perform cardiac assessment with LVEF at baseline and throughout therapy. Following completion of therapy in EBC, monitor for cardiomyopathy every 6 months for at least 2 years. Drug has not been studied in baseline LVEF < 55% EBC or < 50% MBC; prior history of CHF, uncontrolled HTN, recent MI, cumulative anthracycline exposure > 360 mg/m2 of doxorubicin or equivalent or serious cardiac arrhythmia requiring treatment Embryo-Fetal Toxicity. May cause fetal harm when administered in pregnancy. Verify pregnancy status prior to start of therapy. Advise patients regarding effective contraception during treatment and for 7 months after last done. Pulmonary Toxicity. Serious and fatal pulmonary toxicity may result from therapy. Patients with intrinsic lung disease or tumor involvement of the lungs appear to have more severe toxicity Exacerbation of chemotherapy-induced neutropenia. In randomized trials with IV trastuzumab, severe neutropenia and febrile neutropenia was higher among patients receiving both trastuzumab plus chemotherapy compared to those receiving chemotherapy alone. Hypersensitivity and Administration-Related Reactions. Severe HS and ARRs have been associated with IV pertuzumab and trastuzumab. Those with dyspnea at risk due to advanced malignancy and comorbidities may be at increased risk of a severe event. ARRs were reported in 21% of patients receiving PHESGO. The most common reactions were injection site reaction (15%) and injection site pain (2%). Close monitoring of patients is recommended during and for 30 minutes following the initial injection, then monitor during and for 15 minutes following subsequent injections of the maintenance doses. Consider pre-medications for patients experiencing reversible Grade 1 or 2 hypersensitivity reactions with an analgesic, anti-pyretic or antihistamine.
Adverse reactions	Neoadjuvant and adjuvant setting SAEs 16%: FN 4%, neutropenic sepsis 1% DC 8%: reduced LVEF 1.2%, cardiac failure 0.8%, pneumonitis/pulmonary fibrosis 0.8% Dose interruptions 40%: neutropenia 8%, ↓ ANC 4%, diarrhea 7% Metastatic breast cancer setting Diarrhea, alopecia, neutropenia, nausea, fatigue, rash, peripheral neuropathy

Projected Place in Therapy

- PHESGO is a combination product that contains pertuzumab, trastuzumab along with hyaluronidase, an endoglycosidase, for subcutaneous dispersion.
- It has been FDA approved in multiple breast cancer settings where HER2-directed therapies have a key role in the treatment plan.
- Patients currently receiving IV pertuzumab and trastuzumab can transition to subcutaneous pertuzumab, trastuzumab, hyaluronidase. Depending on time since last dose, patient may need a loading vs. maintenance dose.
- The FeDeriCa trial demonstrated that the fixed-dose combination product was non-inferior to intravenous pertuzumab (primary endpoint) as well as IV trastuzumab (secondary endpoint) prior to cycle #8 (i.e. steady state) in the neoadjuvant therapy setting. Total pathological complete response rates were comparable.
- The PHranceSCa study focused on patient preferences. The majority of patients included in this trial preferred the subcutaneous formulation for the main reason of reduced clinic time. Those who preferred the intravenous formulations cited comfort during administration and less injection site pain as their reasons.
- Other advantages of the subcutaneous formulation include:
    - Fixed-dose, which is likely to minimize medication error potential secondary to miscalculations as well as minimize drug waste;
    - Shortened drug infusion time, which equates to less clinic time and less chair space;
    - Less drug preparation time and ancillary equipment (i.e. IV tubing, diluent bags, etc.)
    - Patient IV access site
    - Minimize patient contact and thus exposure to clinic/public areas
- Disadvantages of the subcutaneous formulation include:
    - Greater risk of injection site reactions compared to IV administration
    - No published evidence for use in solid malignancies other than breast cancer
        - There is evidence to support use of the IV pertuzumab-trastzumab combination in the management of HER2-positive GI malignancies.
        - The desire to benefit from advantages of the subcutaneous formulation is expected to impact other disease states that have not been studied.
        - Adjudication for off label uses can be managed at the local facility level on a case-by-case basis.

References/Contact Information

PHESGO Prescribing Information. Genentech, Inc. 2020.

AR, et al. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomized, open-label, multicenter, non-inferiority phase 3 study. Lancet Oncol 2021; 22: 85.

O'Shaughnessy J, Sousa S, Cruz J, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): A randomised, open-label phase II study. European J of Cancer 2021; 152: 223-232.

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