

**Dear Healthcare Professional,**

We are writing to inform you that on June 29, 2020, the Food and Drug Administration (FDA) approved PHESGO™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf) injection, for subcutaneous use. PHESGO is a fixed-dose combination of pertuzumab and trastuzumab, HER2/neu receptor antagonists, and hyaluronidase, an endoglycosidase.<sup>1</sup>

**Indications**

**Early Breast Cancer**

PHESGO™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf) is indicated for use in combination with chemotherapy for

- the 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) as part of a complete treatment regimen for early breast cancer (EBC)
  - the adjuvant treatment of adult patients with HER2-positive early breast cancer (EBC) at high risk of recurrence
- Select patients for therapy based on an FDA-approved companion diagnostic test.

**Metastatic Breast Cancer**

PHESGO™ is indicated for use in combination with docetaxel for the treatment of adult patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Select patients for therapy based on an FDA-approved companion diagnostic test.

**Important Safety Information**

**BOXED WARNINGS: Cardiomyopathy, Embryo-Fetal Toxicity, and Pulmonary Toxicity**

- **PHESGO administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving PHESGO with anthracycline-containing chemotherapy regimens. Evaluate cardiac function prior to and during treatment with PHESGO. Discontinue PHESGO treatment in patients receiving adjuvant therapy and withhold PHESGO in patients with metastatic disease for clinically significant decrease in left ventricular function**
- **Exposure to PHESGO can result in embryo-fetal death and birth defects, including oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**
- **PHESGO administration can result in serious and fatal pulmonary toxicity. Discontinue PHESGO for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve**

**Packaging Information**

Packaging	Dosage and Strength	NDC
1 ready-to-use vial	1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase per 15 mL	NDC 50242-0245-01
1 ready-to-use vial	600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase per 10 mL	NDC 50242-0260-01

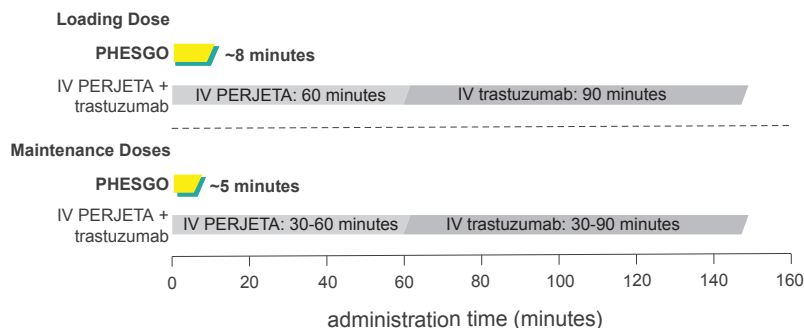
<sup>1</sup> Please see additional Important Safety Information on pages 4-6.

## Coding and Billing Information

TYPE	CODE	DESCRIPTION
Diagnosis: ICD-10-CM	C50.011–C50.019 C50.111–C50.119 C50.211–C50.219 C50.311–C50.319 C50.411–C50.419 C50.511–C50.519 C50.611–C50.619 C50.811–C50.819 C50.911–C50.919	Malignant neoplasm of the female breast
	C50.021–C50.029 C50.121–C50.129 C50.221–C50.229 C50.321–C50.329 C50.421–C50.429 C50.521–C50.529 C50.621–C50.629 C50.821–C50.829 C50.921–C50.929	Malignant neoplasm of the male breast
Drug: HCPCS code	J3490	Not otherwise classified drugs
	J3590	Not otherwise classified biologics
	J9999	Not otherwise classified anti-neoplastic
	C9399	Unclassified or biologics (hospital outpatient only)
Drug: NDC	50242-0245-01	1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase per 15 mL
	50242-0260-01	600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase per 10 mL
Administration procedures: CPT	96401	Chemotherapy administration, subcutaneous or intramuscular; non-hormonal anti-neoplastic
Billable units	For miscellaneous HCPCS codes, 1 billable unit is generally equal to 1 dose. Payers might have different preferences for billing for PHESGO. Check with your local payers for specific billing unit information.	

CPT=Current Procedural Terminology; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; NDC=National Drug Code.

### PHESGO is a ~5 or ~8 minute subcutaneous injection compared with trastuzumab + pertuzumab IV administration, which can take 1 to 2½ hours<sup>1-3\*</sup>



IV=intravenous.

\*Refers to actual injection time of PHESGO vs infusion time of PERJETA IV + trastuzumab IV and does not account for all aspects of treatment. Does not include observation time. Actual clinic time may vary. PERJETA and trastuzumab can be given in any order.<sup>1,2</sup> Please see the PERJETA IV + trastuzumab IV full Prescribing Information for additional dosing information.

Please see PHESGO full Prescribing Information for complete dosing and administration information.

## Contraindications

PHESGO is contraindicated in patients with known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or to any of its excipients.

2 Please see additional Important Safety Information on pages 4-6.

### Fixed-dose PHESGO requires<sup>1</sup>:

- NO reconstitution
- NO dilution
- NO weight adjustments
- NO IV loading dose
- NO port access with a subcutaneous injection

**Patients currently receiving IV PERJETA + trastuzumab can be transitioned to PHESGO if eligible.<sup>1</sup>**

## **PHESGO Clinical Trial Program**

### **PHESGO FDA approval was based on the results from the FeDeriCa study<sup>1</sup>**

**Study Design:** The FeDeriCa study (NCT03493854) was an open-label, multi-center, randomized study conducted in 500 patients with operable or locally advanced (including inflammatory) HER2-positive breast cancer with a tumor size >2 cm or node-positive. HER2 overexpression was defined as IHC 3+ in >10% of immunoreactive cells or HER2 gene amplification by ISH (ratio of HER2 gene signals to centromere 17 signals  $\geq 2.0$ ) using an FDA-approved test. Patients were randomized to receive 8 cycles of neoadjuvant chemotherapy with concurrent administration of 4 cycles of either PHESGO or intravenous pertuzumab and trastuzumab during cycles 5-8, followed by surgery.

Investigators selected one of two of the following neoadjuvant chemotherapy regimens for individual patients:

- 4 cycles of doxorubicin (60 mg/m<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) every 2 weeks followed by paclitaxel (80 mg/m<sup>2</sup>) weekly for 12 weeks
- 4 cycles of doxorubicin (60 mg/m<sup>2</sup>) and cyclophosphamide (600 mg/m<sup>2</sup>) every 3 weeks followed by 4 cycles of docetaxel (75 mg/m<sup>2</sup> for the first cycle and then 100 mg/m<sup>2</sup> at subsequent cycles at the investigator's discretion) every 3 weeks

Following surgery, patients continued therapy with PHESGO or intravenous pertuzumab and trastuzumab as treated prior to surgery, for an additional 14 cycles, to complete 18 cycles of anti-HER2 therapy. Patients also received adjuvant radiotherapy and endocrine therapy as per investigator's discretion. In adjuvant period, substitution of intravenous trastuzumab for subcutaneous trastuzumab was permitted at investigator discretion. Patients received HER2-targeted therapy every 3 weeks.

FeDeriCa was designed to demonstrate noninferiority of the cycle 7 (ie, predose cycle 8) pertuzumab serum C<sub>trough</sub> from PHESGO pertuzumab to the intravenous pertuzumab (primary endpoint). Secondary endpoints included cycle 7 serum trastuzumab C<sub>trough</sub>, efficacy (pathological complete response [pCR], defined as the absence of invasive neoplastic cells in the breast and in the axillary lymph nodes), and safety. The median age was 51 years, and the majority of patients were White (66%). The majority of patients had hormone receptor-positive disease (61%) or node-positive disease (58%).

### **Results**

- In the primary endpoint analysis, PHESGO (n=248) was noninferior to trastuzumab + pertuzumab IV (n=252) based upon pharmacokinetic endpoints
  - Pertuzumab cycle 7 C<sub>trough</sub> (ie, predose cycle 8) showed noninferiority of pertuzumab within PHESGO (88.7 mcg/mL) to intravenous pertuzumab (72.4 mcg/mL), with a geometric mean ratio of 1.22 (90% CI: 1.14-1.31)
- Total pathological complete response (tpCR), a secondary endpoint measuring efficacy, was 59.7% for PHESGO (n=248) and 59.5% for IV PERJETA + trastuzumab (n=252)
- Comparable safety was observed between both arms
  - Incidences of the most common adverse events (occurring in  $\geq 30\%$  of patients): alopecia [(71% in the IV PERJETA + trastuzumab arm (n=252) and 77% in the PHESGO arm) (n=248)], nausea (61% and 60%), diarrhea (57% and 60%), anemia (43% and 36%), and asthenia (32% and 31%)
  - In the FeDeriCa trial, serious adverse reactions occurred in 16% of patients who received PHESGO. Serious adverse reactions in >1% of patients included febrile neutropenia (4%), neutropenic sepsis (1%), and neutrophil count decreased (1%). One fatal adverse reaction occurred in 1/248 (0.4%) of patients, which was due to acute myocardial infarction, and occurred prior to the start of HER2-targeted treatment with PHESGO.

## Most patients in the PHranceSCa trial preferred subcutaneous administration with PHESGO over IV administration with trastuzumab + pertuzumab<sup>1</sup>

**Study Design:** The PHranceSCa study (NCT03674112) is a randomized, multi-center, open-label, cross-over trial conducted in 160 patients with HER2-positive breast cancer undergoing adjuvant treatment. All patients completed neoadjuvant treatment with pertuzumab, trastuzumab, and chemotherapy and had surgery before randomization. Following randomization, 80 patients in Arm A received 3 cycles of intravenous pertuzumab and trastuzumab followed by 3 cycles of PHESGO, and 80 patients in Arm B received 3 cycles of PHESGO followed by 3 cycles of intravenous pertuzumab and trastuzumab. All patients received 18 total cycles of HER2-targeted therapy.

### Results

- 85% of patients (n=136) preferred using PHESGO, citing administration required less time in the clinic as the most common reason<sup>†</sup>
- 14% of patients (n=22) preferred using IV PERJETA + trastuzumab, citing more comfort during administration as the most common reason<sup>†</sup>
- 1% of patients (n=2) had no preference<sup>†</sup>

<sup>†</sup>When surveyed after cycle 6 of adjuvant treatment.

If you have questions or would like more information about PHESGO, please email Genentech at [phesgosupport@gene.com](mailto:phesgosupport@gene.com).

## Important Safety Information

### **BOXED WARNINGS: Cardiomyopathy, Embryo-Fetal Toxicity, and Pulmonary Toxicity**

- **PHESGO administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving PHESGO with anthracycline-containing chemotherapy regimens. Evaluate cardiac function prior to and during treatment with PHESGO. Discontinue PHESGO treatment in patients receiving adjuvant therapy and withhold PHESGO in patients with metastatic disease for clinically significant decrease in left ventricular function**
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- **PHESGO administration can result in serious and fatal pulmonary toxicity. Discontinue PHESGO for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve**

## Contraindications

PHESGO is contraindicated in patients with known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or to any of its excipients.

## Additional Important Safety Information

### **Cardiomyopathy and Cardiac Monitoring**

- PHESGO administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving PHESGO with anthracycline-containing chemotherapy regimens
- Discontinue PHESGO treatment in patients receiving adjuvant therapy and withhold PHESGO in patients with metastatic disease for clinically significant decrease in left ventricular function
- Evaluate cardiac function prior to and during treatment. For adjuvant therapy, also evaluate cardiac function after completion of PHESGO
- Monitor frequently for decreased left ventricular function during and after PHESGO treatment. Monitor more frequently if PHESGO is withheld for significant left ventricular cardiac dysfunction

## Important Safety Information (cont'd)

### Embryo-Fetal Toxicity

- PHESGO can cause fetal harm when administered to a pregnant woman
- Verify the pregnancy status of females of reproductive potential prior to the initiation of PHESGO. Advise pregnant women and females of reproductive potential that exposure to PHESGO during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PHESGO
- There is a pregnancy pharmacovigilance program for PHESGO. If PHESGO is administered during pregnancy, or if a patient becomes pregnant while receiving PHESGO or within 7 months following the last dose of PHESGO, health care providers and patients should immediately report PHESGO exposure to Genentech at 1-888-835-2555

### Pulmonary Toxicity

- PHESGO can cause serious and fatal pulmonary toxicity. These adverse reactions have been reported with intravenous trastuzumab
- Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. 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

### Exacerbation of Chemotherapy-Induced Neutropenia

- PHESGO may exacerbate chemotherapy-induced neutropenia. In randomized controlled clinical trials with intravenous trastuzumab, Grade 3-4 neutropenia and febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone

### Hypersensitivity and Administration-Related Reactions

- Severe administration-related reactions (ARRs), including hypersensitivity, anaphylaxis, and events with fatal outcomes, have been associated with intravenous pertuzumab and trastuzumab. Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a severe or of a fatal ARR
- In the FeDeriCa study, the incidence of hypersensitivity was 1.2% in the PHESGO arm. ARRs occurred in 21% of patients who received PHESGO. In the PHESGO arm, the most common administration-related reactions were injection site reaction (15%) and injection site pain (2%)
- Closely monitor patients during and for 30 minutes after the injection of initial dose and during and for 15 minutes following subsequent injections of maintenance dose of PHESGO. If a significant injection-related reaction occurs, slow down or pause the injection and administer appropriate medical therapies. Evaluate and carefully monitor patients until complete resolution of signs and symptoms
- Permanently discontinue treatment with PHESGO in patients who experience anaphylaxis or severe injection-related reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. For patients experiencing reversible Grade 1 or 2 hypersensitivity reactions, consider pre-medication with an analgesic, antipyretic, or an antihistamine prior to readministration of PHESGO

## Important Safety Information (cont'd)

### Most Common Adverse Reactions

#### Early Breast Cancer

The most common adverse reactions (>30%) with PHESGO were alopecia, nausea, diarrhea, anemia, and asthenia.

#### Metastatic Breast Cancer (based on IV pertuzumab)

The most common adverse reactions (>30%) with pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy.

You are encouraged to report side effects to Genentech and the FDA. You may report side effects to the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). You may also report side effects to Genentech at 1-888-835-2555.

**Please see full Prescribing Information for additional Important Safety Information, including BOXED WARNINGS.**

Regards,

**Genentech**

*A Member of the Roche Group*

**PHESGO**<sup>™</sup>   
pertuzumab/trastuzumab/hyaluronidase-zzxf  
SUBCUTANEOUS INJECTION / 1,200 mg/600 mg/30,000 units  
600 mg/600 mg/20,000 units

**References:** **1.** PHESGO (pertuzumab, trastuzumab, and hyaluronidase-zzxf). Prescribing Information. Genentech, Inc. 2020. **2.** PERJETA Prescribing Information. Genentech, Inc. 2020. **3.** Herceptin Prescribing Information. Genentech, Inc. 2018.