PHESGO—a combination with PERJETA® (pertuzumab) & Herceptin® (trastuzumab) in a single ~5 minute injection under the skin.*

*Your first dose is given in ~8 minutes. This does not account for observation time and other aspects of treatment. Actual clinic time may vary.

**What does PHESGO treat?**

PHESGO® (pertuzumab, trastuzumab, and hyaluronidase-zzxf) is a prescription medicine approved for use in combination with chemotherapy for:

- use prior to surgery (neoadjuvant treatment) in adults with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (tumor is greater than 2 cm in diameter or node-positive). PHESGO should be used as part of a complete treatment regimen for early breast cancer.
- use after surgery (adjuvant treatment) in adults with HER2-positive early breast cancer that has a high likelihood of coming back.

PHESGO is a prescription medicine approved for use in combination with docetaxel in adults who have HER2-positive breast cancer that has spread to different parts of the body (metastatic) and who have not received anti-HER2 therapy or chemotherapy for metastatic breast cancer.

**Important Safety Information**

**What are the most serious side effects of PHESGO?**

- PHESGO may cause heart problems, including those without symptoms (such as reduced heart function) and those with symptoms (such as congestive heart failure)
- Receiving PHESGO during pregnancy can result in the death of an unborn baby and birth defects
- PHESGO may cause serious lung problems

Please see Important Safety Information on pages 5-6 and full Prescribing Information, including most serious side effects.

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What is PHESGO?

PHESGO is an injection given just under the skin. There are 2 medicines inside PHESGO: PERJETA® (pertuzumab) and Herceptin® (trastuzumab). PHESGO also contains a protein called hyaluronidase that helps your body absorb the 2 medicines and allows them to be given as a single injection in about 5 minutes.*

PHESGO is given as part of a complete treatment regimen for HER2+ breast cancer that includes chemotherapy.

*Your first dose is given in ~8 minutes. This does not account for observation time and other aspects of treatment. Actual clinic time may vary.

So the main difference between PHESGO & PERJETA + Herceptin is how it’s given?

Yes. PERJETA and Herceptin are given as 2 separate infusions, either through an IV (a method of administering a drug by inserting a needle into a vein) or through a port. PHESGO is given as one injection just under the skin in the thigh.

How does PHESGO work?

You may be wondering how hours of infusion can be given in just minutes. Well, PHESGO is specially designed with hyaluronidase, a natural protein found in most tissues of the body.

Hyaluronidase helps enhance the way the body absorbs medicines injected under the skin. Once PHESGO is absorbed by your body, it’s thought to work the same way as PERJETA + Herceptin to treat your HER2+ breast cancer.

By taking PHESGO, you’re taking the same medicines as PERJETA and Herceptin—*they just take less time.*

maintenance dose time

0 1 hr 2 hr

1.25 hours for PERJETA + Herceptin infusion

This does not account for observation time and other aspects of treatment. Actual clinic time may vary.

Ask your doctor if starting treatment with PHESGO is right for you.

Please see Important Safety Information on pages 5-6 and full Prescribing Information, including most serious side effects.
Does PHESGO work as well as PERJETA + Herceptin?

PHESGO was studied in comparison to IV PERJETA® (pertuzumab) + Herceptin® (trastuzumab).* This clinical study included 500 people with certain types of HER2+ early breast cancer. Everyone in the study also received chemotherapy as part of a complete treatment regimen.

The goal of the study was to find out if there were any differences between PHESGO and PERJETA + Herceptin. This study measured the amount of medicine in the bloodstream, which is commonly done to check that the injection works like the infusion. The study also looked at how safe the drug was and if it worked on the cancer.

In this study, no major difference was seen in the amount of medicine that went into the bloodstream with PHESGO compared to PERJETA + Herceptin. The combined results of the study showed that no major difference is expected in how it works.

*Some patients in the trial were given Herceptin HYLECTA™ (trastuzumab and hyaluronidase-oysk) injections instead of Herceptin infusions during treatment after surgery.

More people preferred PHESGO over PERJETA + Herceptin

In another clinical study, 160 people with HER2+ early breast cancer were asked questions to find out which treatment they preferred. They were given IV PERJETA + Herceptin + chemotherapy before surgery. After surgery, some were given 3 cycles of IV PERJETA + Herceptin then 3 cycles of PHESGO. Others were given PHESGO first then IV PERJETA + Herceptin. Everyone completed a total of 18 cycles of treatment. Patients were asked which treatment they preferred after they completed 6 cycles.

The most common reason people preferred PHESGO was because it took less time in the clinic.

- The most common reason people preferred IV PERJETA + Herceptin was because it felt more comfortable during administration.

Important Safety Information (cont’d)

What are other possible serious side effects?

- PHESGO should not be used in patients who are allergic to pertuzumab, trastuzumab, hyaluronidase, or to any of the ingredients in PHESGO.
- Other possible serious and sometimes fatal side effects of PHESGO therapy include:
  - Worsening of low white blood cell counts caused by chemotherapy
  - Severe allergic reactions (hypersensitivity reactions/anaphylaxis) and administration-related reactions

Please see Important Safety Information on pages 5-6 and full Prescribing Information, including most serious side effects.
How is PHESGO given?

PHESGO is always given by a healthcare professional. PHESGO is administered by slowly injecting it under the skin of the thigh. At each visit, they should alternate between the left and right thigh.

Tip: Wear loose shorts or a skirt for your appointment so your healthcare provider can easily access your thigh for injection. It’s a good idea to bring a blanket, too, to stay warm.

Since it’s an injection under the skin, PHESGO does not require port access.

Injection time

1st Injection
~8 mins
15 mins

Other Injections
~5 mins
30 mins

Your healthcare team will wait at least 30 minutes after the first dose, and at least 15 minutes after each following dose, to check for any reactions. If side effects occur, your healthcare provider may slow, delay, or stop your treatment.

Treatment schedule

If you are taking PHESGO for early breast cancer, you will take it every 3 weeks for a total of 1 year (up to 18 cycles) unless side effects become too difficult to manage or the cancer comes back sooner. Depending on the treatment plan your doctor creates for you, you may start PHESGO before surgery or after surgery.

If you are taking PHESGO for metastatic breast cancer, you will take it every 3 weeks until the cancer progresses or side effects become too difficult to manage.

You should also get chemotherapy as part of a complete treatment regimen with PHESGO. Talk to your doctor for more information about your chemotherapy schedule.

What if I miss an injection?

If you miss a dose of PHESGO, DO NOT WAIT until your next treatment. Contact your doctor or nurse right away and work with them to reschedule the treatment you missed.

Can I switch from PERJETA + Herceptin to PHESGO?

Yes, your doctor may be able to switch you from PERJETA® (pertuzumab) + Herceptin® (trastuzumab) to PHESGO. Talk to your doctor about your options.

Please see Important Safety Information on pages 5-6 and full Prescribing Information, including most serious side effects.
Important Safety Information

What should I know about side effects with PHESGO?

• Not all people have serious side effects; however, side effects with PHESGO therapy are common. It is important to know what side effects may happen and what symptoms you should watch for
• Your doctor may stop treatment if serious side effects happen. Be sure to contact your healthcare team right away if you have questions or are worried about any side effects

What are the most serious side effects of PHESGO?

PHESGO may cause heart problems, including those without symptoms (such as reduced heart function) and those with symptoms (such as congestive heart failure).

• The risk for and seriousness of these heart problems are highest in people who received both PHESGO and a certain type of chemotherapy (anthracycline)
• Your doctor will check for signs of heart problems before, during, and after treatment with PHESGO. Based on test results, your doctor may hold or discontinue treatment with PHESGO
• Contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness

Receiving PHESGO during pregnancy can result in the death of an unborn baby and birth defects.

• Birth control should be used while receiving PHESGO and for 7 months after your last dose of PHESGO. If you are a mother who is breastfeeding, you should talk with your doctor about either stopping breastfeeding or stopping PHESGO
• If you think you may be pregnant, you should contact your healthcare provider immediately
• If you are exposed to PHESGO during pregnancy, or become pregnant while receiving PHESGO or within 7 months following the last dose of PHESGO, you are encouraged to report PHESGO exposure to Genentech at 1-888-835-2555

PHESGO may cause serious lung problems.

• Your doctor may check for signs of lung problems including:
  – Severe shortness of breath
  – Fluid in or around the lungs
  – Weakening of the valve between the heart and the lungs
  – Not enough oxygen in the body
  – Swelling of the lungs
  – Scarring of the lungs

Who should not receive PHESGO?

• PHESGO should not be used in patients who are allergic to pertuzumab, trastuzumab, hyaluronidase, or to any of the ingredients in PHESGO

Continued on next page.
Important Safety Information (cont’d)

What are other possible serious side effects?

• PHESGO may worsen low white blood cell counts caused by chemotherapy: Low white blood cell counts can be life threatening and were seen more often in patients receiving Herceptin® (trastuzumab) plus chemotherapy than in patients receiving chemotherapy alone. Your doctor may check for signs of low white blood cell counts when he or she examines you.

• PHESGO may cause administration-related reactions: PHESGO is given as an injection. The active ingredients in PHESGO have been associated with severe administration reactions, including hypersensitivity or anaphylaxis, which can be fatal. Talk to your doctor if you feel any symptoms. The most common symptoms include dizziness, nausea, chills, fever, vomiting, diarrhea, urticaria, angioedema, breathing problems, or chest pain.

What are the most common side effects?

The most common side effects of PHESGO when given with chemotherapy as part of an early breast cancer regimen are:

• Hair Loss
• Nausea
• Diarrhea
• Low levels of red blood cells
• Weakness

The most common side effects of PHESGO when given with docetaxel for treatment of breast cancer that has spread to other parts of the body (metastatic) are:

• Diarrhea
• Hair loss
• Low levels of white blood cells with or without fever
• Nausea
• Feeling tired
• Rash
• Damage to the nerves (numbness, tingling, pain in hands/feet)

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. You may also report side effects to Genentech at 1-888-835-2555.

Talk to a healthcare professional for more information about the benefits and risks of PHESGO.

Please see full Prescribing Information for additional Important Safety Information, including most serious side effects.

If you cannot afford your medication, visit genentech-access.com/patient for financial assistance information.
Start the conversation with your healthcare team about PHESGO

To better understand PHESGO, and a potential PHESGO treatment plan, it helps to have a detailed discussion with your healthcare team.

Here are some questions to help you get started.

1. Is treatment with PHESGO right for me?
2. What can I expect during treatment with PHESGO?
3. How is PHESGO different from PERJETA® (pertuzumab) + Herceptin® (trastuzumab)?
4. Can I switch from PERJETA + Herceptin to PHESGO?
5. Do I take PHESGO with chemotherapy?
6. Where will I get my treatment?
7. How do I prepare for my treatment?
8. What should I wear on treatment days?
9. How long will I get PHESGO?
10. How long will I get chemotherapy?
11. What potential side effects should I expect or know about?
12. How might my side effects be different once I finish chemotherapy when I’m only getting PHESGO?
13. How will my doctor know if my treatment is working?

Notes

Who to call: ________________________________
How to reach them: __________________________
When to call: ________________________________

Please see Important Safety Information on pages 5-6 and full Prescribing Information, including most serious side effects.
Genentech Patient Support Services

When your doctor prescribes a Genentech medicine, we have programs that can help based on your unique needs.

General patient inquiries

The Genentech Patient Resource Center is ready to help people who have questions about PHESGO and support options.

Please call the Genentech Patient Resource Center at (877)-GENENTECH / (877)-436-3683 for more information.

Treatment education and support

HERConnection is a free HER2+ breast cancer support program for people taking Genentech medicines. It could help you navigate your PHESGO treatment journey by providing you with useful information, tips for healthy living, and free tools to use along the way.

Visit HERConnection.com to see what you’ll get and sign up.

Help understanding insurance coverage and costs

Genentech Access Solutions works with your doctor, health insurance company, and specialty pharmacy to help you get your Genentech medicine.

Visit genentech-access.com/phesgo/patients

The Genentech Patient Foundation gives you your Genentech medicine for free, if you’re eligible.

To learn more and to apply for help visit GenentechPatientFoundation.com

Genentech co-pay programs may help you if you have commercial health insurance* and meet other eligibility criteria.

We can refer you to an independent co-pay assistance foundation. This is a charitable organization that may give financial help for medicines.

To learn more about the Genentech Oncology Co-pay Assistance Program or to get the full list of terms and conditions visit www.copayassistancenow.com

*This might be a plan you get through your employer or one you purchased through a Health Insurance Marketplace like HealthCare.gov.

Please see Important Safety Information on pages 5-6 and full Prescribing Information, including most serious side effects.
THE TIME IS NOW

Talk to your doctor about your treatment options today.
PHESGO (pertuzumab, trastuzumab, and hyaluronidase-zxxf) injection, for subcutaneous use

Initial U.S. Approval: 2020

**INDICATIONS AND USAGE**

PHESGO is a combination of pertuzumab and trastuzumab, HER2/neu receptor antagonists, and hyaluronidase, an endoglycosidase, indicated for:

- Neoadjuvant and adjuvant 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. (1.1)
- Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence. (1.1)

Use in combination with docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. (1.2)

**DOSEAGE AND ADMINISTRATION**

- For subcutaneous use in the thigh only.
- PHESGO has different dosage and administration instructions than intravenous pertuzumab and trastuzumab products.
- Do not administer intravenously. (2.2)
- Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1.2.1)

- The initial dose of PHESGO is 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase administered subcutaneously over approximately 8 minutes, followed every 3 weeks by a dose of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase administered subcutaneously over approximately 5 minutes. (2.2)
- Neoadjuvant: administer PHESGO by subcutaneous injection every 3 weeks and chemotherapy by intravenous infusion preoperatively for 3 to 6 cycles. (2.2)
- Adjuvant: administer PHESGO by subcutaneous injection every 3 weeks and chemotherapy by intravenous infusion postoperatively for a total of 1 year (up to 18 cycles). (2.2)
- MBC: administer PHESGO by subcutaneous injection and docetaxel by intravenous infusion every 3 weeks. (2.2)

**CONTRAINdications**

PHESGO is contraindicated in patients with known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or to any of its excipients. (4)

**WARNINGS AND PRECAUTIONS**

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.4)
- Hypersensitivity and Administration-Related Reactions (ARRs): Monitor patients for systemic hypersensitivity reactions. Permanently discontinue PHESGO in patients who experience anaphylaxis or severe hypersensitivity reactions. (5.5)

**ADVERSE REACTIONS**

- Neoadjuvant and Adjuvant Treatment of Breast Cancer
- The most common adverse reactions (>30%) with PHESGO were alopecia, nausea, diarrhea, anemia, and asthenia. (6.1)
- Metastatic Breast Cancer (based on intravenous 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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of PHESGO. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2020
FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CARDIOMYOPATHY, EMBRYO-FETAL TOXICITY, AND PULMONARY TOXICITY

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1 INDICATIONS AND USAGE

1.1 Early Breast Cancer (EBC)

PHESGO 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 [see Dosage and Administration (2.2) and Clinical Studies (14.2)].
- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence [see Dosage and Administration (2.2) and Clinical Studies (14.2)].

Select patients for therapy based on an FDA-approved companion diagnostic test [see Dosage and Administration (2.1)].

1.2 Metastatic Breast Cancer (MBC)

PHESGO is indicated for use in combination with docetaxel for the treatment of adult patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease [see Dosage and Administration (2.2) and Clinical Studies (14.1)].

Select patients for therapy based on an FDA-approved companion diagnostic test [see Dosage and Administration (2.1)].
2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection
Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Important Dosage and Administration Information
PHESGO is for subcutaneous use only in the thigh. Do not administer intravenously.

PHESGO has different dosage and administration instructions than intravenous pertuzumab, intravenous trastuzumab, and subcutaneous trastuzumab when administered alone.

Do not substitute PHESGO for or with pertuzumab, trastuzumab, ado-trastuzumab emtansine, or fam-trastuzumab deruxtecan.

PHESGO must always be administered by a healthcare professional.

In patients receiving an anthracycline-based regimen for early breast cancer, administer PHESGO following completion of the anthracycline.

In patients receiving PHESGO for early breast cancer with docetaxel or paclitaxel, administer docetaxel or paclitaxel after PHESGO.

In patients receiving PHESGO for metastatic breast cancer with docetaxel, administer docetaxel after PHESGO.

Observe patients for a minimum of 30 minutes after initial dose of PHESGO and 15 minutes after each maintenance dose of PHESGO for signs or hypersensitivity symptoms or administration-related reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use [see Warnings and Precautions (5.5)].

2.3 Recommended Doses and Schedules
The recommended dosage and administration schedule for PHESGO are shown in Table 1.

Table 1: Recommended Dosage and Administration Schedule

<table>
<thead>
<tr>
<th>Dose</th>
<th>Strength</th>
<th>Administration Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial dose</strong></td>
<td>1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase in 15 mL (1,200 mg, 600 mg, and 30,000 units/15 mL)</td>
<td>Administer subcutaneously over approximately 8 minutes</td>
</tr>
<tr>
<td><strong>Maintenance dose</strong> (administer every 3 weeks)</td>
<td>600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase in 10 mL (600 mg, 600 mg, and 20,000 units/10 mL)</td>
<td>Administer subcutaneously over approximately 5 minutes every 3 weeks</td>
</tr>
</tbody>
</table>
No dose adjustments for PHESGO are required for patient body weight or for concomitant chemotherapy regimen.

Patients currently receiving intravenous pertuzumab and trastuzumab can transition to PHESGO. In patients receiving intravenous pertuzumab and trastuzumab with < 6 weeks since their last dose, administer PHESGO as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab and every 3 weeks for subsequent administrations. In patients receiving intravenous pertuzumab and trastuzumab with ≥ 6 weeks since their last dose, administer PHESGO as an initial dose of 1,200 mg pertuzumab/600 mg trastuzumab, followed by a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks for subsequent administrations.

Neoadjuvant Treatment of Breast Cancer

Administer PHESGO every 3 weeks for 3 to 6 cycles as part of a treatment regimen for early breast cancer [see Clinical Studies (14.2)].

Refer to the prescribing information for pertuzumab, administered in combination with trastuzumab and chemotherapy, for recommended dose and dosage modifications.

Following surgery, patients should continue to receive PHESGO to complete 1 year of treatment (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as a part of a complete regimen for early breast cancer.

Adjuvant Treatment of Breast Cancer

Administer PHESGO every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. Start PHESGO on Day 1 of the first taxane-containing cycle [see Clinical Studies (14.2)].

Metastatic Breast Cancer (MBC)

When administered with PHESGO, the recommended initial dose of docetaxel is 75 mg/m² administered as an intravenous infusion. The dose may be escalated to 100 mg/m² administered every 3 weeks if the initial dose is well tolerated. Administer PHESGO until disease progression or unmanageable toxicity, whichever occurs first.

2.4 Dose Modification

Dose Modification for delayed or missed doses

For delayed or missed doses of PHESGO, 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.

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.

For chemotherapy dose modifications, see relevant prescribing information.

Cardiomyopathy [see Boxed Warning, Warnings and Precautions (5.1)]

Assess left ventricular ejection fraction (LVEF) prior to initiation of PHESGO and at regular intervals during treatment as indicated in Table 2.

The recommendations on dose modifications in the event of LVEF dysfunction are indicated in Table 2 [see Warnings and Precautions (5.1)].
Table 2: Dose Modifications for Left Ventricular Dysfunction

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

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

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 PHESGO [see Warnings and Precautions (5.1)].

**Hypersensitivity and Administration-Related Reactions**

Discontinue the injection immediately if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) [see Warnings and Precautions (5.5)].

**2.5 Preparation for Administration**

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is PHESGO and not intravenous pertuzumab, or intravenous trastuzumab, or subcutaneous trastuzumab.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vial if particulates or discoloration is present. Do not shake. Discard any unused portion remaining in the vial.

For both the initial and maintenance dose, each corresponding PHESGO vial is ready-to-use for one subcutaneous injection and should not be diluted.

A syringe, a transfer needle, and an injection needle are needed to withdraw PHESGO solution from the vial and inject it subcutaneously. PHESGO may be injected using 25G-27G (3/8”-5/8”) hypodermic injection needles.

To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration followed by volume adjustment to 15 mL (initial dose) and 10 mL (maintenance dose). If the dose is not to be administered immediately, and the solution of PHESGO has been withdrawn from the vial into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe with the peel-off sticker and store the syringe in the refrigerator [2°C to 8°C (36°F to 46°F)] for up to 24 hours and at room temperature [20°C to 25°C (68°F to 77°F)] for up to 4 hours and avoid unnecessary storage.
PHESGO is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride and fluorinated ethylene polypropylene.

**Administration**

- Administer PHESGO 1,200 mg, 600 mg, 30,000 units/15 mL subcutaneously over approximately 8 minutes
- Administer PHESGO 600 mg, 600 mg, 20,000 units/10 mL subcutaneously over approximately 5 minutes

The subcutaneous injection site should be alternated between the left and right thigh only. New injections should be given at least 1 inch (2.5 cm) from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. Do not split the dose between two syringes or between two sites of administration. During the treatment course with PHESGO, other medications for subcutaneous administration should preferably be injected at different sites.

### 3 DOSAGE FORMS AND STRENGTHS

Injection: PHESGO is a clear to opalescent, and colorless to slightly brownish solution provided as:

- 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase/15 mL (80 mg, 40 mg, and 2,000 units/mL) of solution in a single-dose vial
- 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase/10 mL (60 mg, 60 mg, and 2,000 units/mL) of solution in a single-dose vial

### 4 CONTRAINDICATIONS

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

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Cardiomyopathy

PHESGO can cause hypertension, arrhythmias, left ventricular cardiac dysfunction, disabling cardiac failure, cardiomyopathy, and cardiac death [see Boxed Warning: Cardiomyopathy]. PHESGO can cause asymptomatic decline in LVEF.

An increased incidence of LVEF decline has been observed in patients treated with intravenous pertuzumab, intravenous trastuzumab, and docetaxel. A 4-6 fold increase in the incidence of symptomatic myocardial dysfunction has been reported among patients receiving trastuzumab, with the highest absolute incidence occurring when trastuzumab was administered with an anthracycline.

Patients who receive anthracycline after stopping PHESGO may also be at increased risk of cardiac dysfunction [see Drug Interactions (7) and Clinical Pharmacology (12.2)].

**Cardiac Monitoring**

Prior to initiation of PHESGO, conduct a thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan.

During treatment with PHESGO, assess LVEF at regular intervals [see Dosage and Administration (2.4)].

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 PHESGO.

Following completion of PHESGO, continue to monitor for cardiomyopathy and assess LVEF measurements every 6 months for at least 2 years as a component of adjuvant therapy.
In the FeDeriCa study, the percentage of patients with at least one cardiac disorder was 22% in the PHESGO arm. The most frequent cardiac adverse reaction in the PHESGO arm was ejection fraction decreased.

The incidence of cardiac failure (NYHA Class III/IV) with a LVEF decline ≥ 10% and a drop to less than 50% was 0.8% in the PHESGO arm. Confirmed asymptomatic or mildly symptomatic (NYHA Class II) declines in LVEF ≥ 10% and a drop to less than 50% was 1.2% in the PHESGO arm [see Adverse Reactions (6.1)].

PHESGO and/or intravenous pertuzumab and trastuzumab have not been studied in patients with a pretreatment LVEF value of < 55% (EBC) or <50% (MBC); a prior history of CHF, conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m² of doxorubicin or its equivalent.

5.2 Embryo-Fetal Toxicity

PHESGO can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of intravenous trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, administration of intravenous pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal death at exposures 2.5 to 20 times the exposure in humans at the recommended dose, based on C_max.

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 [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.3)].

5.3 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.

5.4 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. The incidence of septic death was similar among patients who received trastuzumab and those who did not.

5.5 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. Administration-related reactions 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 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 [see Adverse Reactions (6.1)].

PHESGO is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab, hyaluronidase or to any of its excipients [see Contraindications (4)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy [see Warnings and Precautions (5.1)]
- Embryo-Fetal Toxicity [see Warnings and Precautions (5.2)]
- Pulmonary Toxicity [see Warnings and Precautions (5.3)]
- Exacerbation of Chemotherapy-Induced Neutropenia [see Warnings and Precautions (5.4)]
- Hypersensitivity and Administration-Related Reactions [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Neoadjuvant and Adjuvant Treatment of Breast Cancer

The safety of PHESGO was evaluated in an open-label, multicenter, randomized study (FeDeriCa) conducted in 500 patients with HER2 overexpressing early breast cancer [see Clinical Studies (14.2)].

Patients were randomized to receive either PHESGO (1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase/15 mL) followed every 3 weeks by a maintenance dose of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase/10 mL or the recommended dosages for intravenous pertuzumab and intravenous trastuzumab. 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. Following surgery, patients continued therapy with PHESGO or intravenous pertuzumab and trastuzumab (intravenous or subcutaneously administered) as treated prior to surgery, for an additional 14 cycles, to complete 18 cycles. The median duration of treatment for PHESGO was 24 weeks (range: 0-42 weeks).

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.

Adverse reactions resulting in permanent discontinuation of any study drug occurred in 8% of patients on the PHESGO arm. Adverse reactions which resulted in permanent discontinuation of PHESGO were ejection fraction decreased (1.2%), cardiac failure (0.8%), and pneumonitis/pulmonary fibrosis (0.8%).

Dosage interruptions due to an adverse reaction occurred in 40% of patients who received PHESGO. Adverse reactions which required dosage interruption in > 1% of patients who received PHESGO included neutropenia (8%), neutrophil count decreased (4%), and diarrhea (7%).

Tables 3 summarizes the adverse reactions in FeDeriCa.

<p>| Table 3: Adverse Reactions (≥ 5%) in Patients Who Received PHESGO in FeDeriCa |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Body System/Adverse Reactions   | PHESGO                          | Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab |
|                                 | (n=248)                         | plus intravenous or subcutaneous trastuzumab                                      |
|                                 | All Grades %                    | Grades 3 – 4 %                     | All Grades %                    | Grades 3 – 4 %                     |
|                                 |                                 |                                 |                                 |                                 |
| Skin and subcutaneous tissue disorders |                                 |                                 |                                 |                                 |
| Alopecia                        | 77                              | 0                               | 71                              | 0.4                             |
| Dry skin                        | 15                              | 0.4                             | 13                              | 0                               |
| Rash                            | 16                              | 0.4                             | 21                              | 0                               |
| Nail discoloration              | 9                               | 0                               | 6                               | 0                               |
| Erythema                        | 9                               | 0                               | 5                               | 0                               |
| Dermatitis                      | 7                               | 0                               | 6                               | 0                               |
| Nail disorder                   | 7                               | 0                               | 7                               | 0.4                             |
| Palmar-plantar erythrodysesthesia syndrome | 6                              | 0.8                             | 5                               | 0.4                             |
| Gastrointestinal disorders      |                                 |                                 |                                 |                                 |
| Nausea                          | 60                              | 2                               | 61                              | 1.6                             |
| Diarrhea                        | 60                              | 7                               | 57                              | 4.8                             |
| Stomatitis                      | 25                              | 0.8                             | 24                              | 0.8                             |
| Constipation                    | 22                              | 0                               | 21                              | 0                               |
| Vomiting                        | 20                              | 0.8                             | 19                              | 1.2                             |
| Dyspepsia                       | 14                              | 0                               | 12                              | 0                               |
| Hemorrhoids                     | 9                               | 0                               | 4.0                             | 0                               |
| Abdominal pain upper            | 8                               | 0                               | 6                               | 0                               |
| Abdominal pain                  | 9                               | 0.4                             | 6                               | 0                               |
| Blood and lymphatic system disorders |                                 |                                 |                                 |                                 |
| Anemia                          | 36                              | 1.6                             | 43                              | 4.4                             |
| Neutropenia                     | 22                              | 14                              | 27                              | 14                              |
| Leukopenia                      | 9                               | 2.4                             | 14                              | 2                               |
| Febrile neutropenia             | 7                               | 7                               | 6                               | 6                               |
| General disorders and administration site conditions | | | | |
| Asthenia                        | 31                              | 0.4                             | 32                              | 2.4                             |</p>
<table>
<thead>
<tr>
<th>Body System/Adverse Reactions</th>
<th>PHESGO (n=248)</th>
<th>Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 – 4 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>15</td>
<td>0.8</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Malaise</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>16</td>
<td>0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>10</td>
<td>0.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>11</td>
<td>0.8</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>25</td>
<td>0.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>15</td>
<td>0.4</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>1.2</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Paronychia</td>
<td>7</td>
<td>0.4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7</td>
<td>0.4</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural pain</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Radiation skin injury</td>
<td>19</td>
<td>0.4</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<p>| Body System/Adverse Reactions                      | PHESGO (n=248) | Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252) |
|                                                  | All Grades %  | Grades 3 – 4 %                                                            |
| Fatigue                                          | 29            | 2                                                                        |
| Mucosal inflammation                             | 15            | 0.8                                                                      |
| Injection site reaction                          | 15            | 0                                                                        |
| Pyrexia                                          | 13            | 0                                                                        |
| Edema peripheral                                 | 8             | 0                                                                        |
| Malaise                                          | 7             | 0                                                                        |
| Influenza-like illness                           | 5             | 0                                                                        |
| Nervous system disorders                         |               |                                                                          |
| Dysgeusia                                        | 17            | 0                                                                        |
| Peripheral sensory neuropathy                    | 16            | 0.8                                                                      |
| Headache                                         | 17            | 0                                                                        |
| Neuropathy peripheral                            | 12            | 0.4                                                                      |
| Paresthesia                                      | 10            | 0.8                                                                      |
| Dizziness                                        | 13            | 0                                                                        |
| Investigations                                   |               |                                                                          |
| Weight decreased                                 | 11            | 0.8                                                                      |
| Musculoskeletal and connective tissue disorders   |               |                                                                          |
| Myalgia                                          | 25            | 0.4                                                                      |
| Arthralgia                                       | 24            | 0                                                                        |
| Back pain                                        | 10            | 0                                                                        |
| Bone pain                                        | 7             | 0                                                                        |
| Pain in extremity                                | 6             | 0                                                                        |
| Muscle spasms                                    | 6             | 0                                                                        |
| Musculoskeletal pain                             | 6             | 0.4                                                                      |
| Respiratory, thoracic and mediastinal disorder   |               |                                                                          |
| Cough                                            | 15            | 0.4                                                                      |
| Epistaxis                                        | 12            | 0                                                                        |
| Dyspnea                                          | 10            | 1.2                                                                      |
| Rhinorrhea                                       | 7             | 0                                                                        |
| Infections and infestations                      |               |                                                                          |
| Upper respiratory tract infection                 | 11            | 0                                                                        |
| Nasopharyngitis                                  | 9             | 0                                                                        |
| Paronychia                                       | 7             | 0.4                                                                      |
| Urinary tract infection                          | 7             | 0.4                                                                      |
| Injury, poisoning and procedural complications    |               |                                                                          |
| Procedural pain                                  | 13            | 0                                                                        |
| Radiation skin injury                            | 19            | 0.4                                                                      |
| Infusion related reaction                        | 3.6           | 0                                                                        |
| Metabolism and nutrition disorders               |               |                                                                          |
| Decreased appetite                               | 17            | 0.8                                                                      |</p>
<table>
<thead>
<tr>
<th>Body System/Adverse Reactions</th>
<th>PHESGO (n=248)</th>
<th>Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 – 4 %</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>Dry eye</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinically relevant adverse reactions in < 5% of patients who received PHESGO include ejection fraction decreased (3.6%) and pruritus (3.2%).

Table 4 summarizes the laboratory abnormalities in FeDeriCa.

**Table 4: Select Laboratory Abnormalities (≥5%) that Worsened from Baseline in Patients Who Received PHESGO in FeDeriCa**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>PHESGO (n=248)</th>
<th>Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 – 4 %</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (low)</td>
<td>90</td>
<td>2.8</td>
</tr>
<tr>
<td>Lymphocytes, Absolute (low)</td>
<td>89</td>
<td>37</td>
</tr>
<tr>
<td>Total Leukocyte Count (low)</td>
<td>82</td>
<td>25</td>
</tr>
<tr>
<td>Neutrophils, Total Absolute (low)</td>
<td>68</td>
<td>30</td>
</tr>
<tr>
<td>Platelet (low)</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (high)</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase (high)</td>
<td>58</td>
<td>1.6</td>
</tr>
<tr>
<td>Aspartate aminotransferase (high)</td>
<td>50</td>
<td>0.8</td>
</tr>
<tr>
<td>Potassium (low)</td>
<td>17</td>
<td>5.2</td>
</tr>
<tr>
<td>Albumin (low)</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Potassium (high)</td>
<td>13</td>
<td>1.2</td>
</tr>
<tr>
<td>Sodium (low)</td>
<td>13</td>
<td>0.4</td>
</tr>
<tr>
<td>Bilirubin (high)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Glucose (low)</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>
Laboratory Abnormality | PHESGO (n=248) | Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (high)</td>
<td>7 % 0.8 %</td>
<td>10 % 0.8 %</td>
</tr>
</tbody>
</table>

1 The denominator used to calculate the rate varied from 163 to 252 based on the number of patients with a baseline value and at least one post-treatment value.

Other Clinical Trials Experience

The safety of the addition of intravenous pertuzumab to trastuzumab in combination with chemotherapy has been established in studies conducted in patients with HER2 overexpressing early breast cancer. The following adverse reactions have been reported following administration of intravenous pertuzumab and trastuzumab: diarrhea, alopecia, nausea, fatigue, neutropenia, vomiting, peripheral neuropathy, constipation, anemia, asthenia, mucosal inflammation, myalgia, and thrombocytopenia. Refer to the Prescribing Information for pertuzumab for more information.

The safety of intravenous pertuzumab, trastuzumab and docetaxel has been established in patients with HER2 overexpressing metastatic breast cancer. The following adverse reactions have been reported following administration of intravenous pertuzumab and trastuzumab: diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. Refer to the Prescribing Information for pertuzumab for more information.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity with PHESGO. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PHESGO and intravenous pertuzumab and trastuzumab in the FeDeriCa study with the incidence of antibodies in other studies or to other products may be misleading.

In the FeDeriCa study, the incidence of treatment-emergent anti-pertuzumab and anti-trastuzumab antibodies in most patients completing 1-4 cycles of therapy was 3% (7/237) and 0.4% (1/237), respectively, in patients treated with intravenous pertuzumab and trastuzumab. The incidence of treatment-emergent anti-pertuzumab, anti-trastuzumab, and anti-recombinant human hyaluronidase PH20 antibodies in most patients completing 1-4 cycles of therapy was 4.8% (11/231), 0.9% (2/232), and 0.9% (2/225), respectively, in patients treated with PHESGO. Among patients who tested positive to anti-pertuzumab antibodies, neutralizing anti-pertuzumab antibodies were detected in one patient treated with intravenous pertuzumab and trastuzumab and in one patient treated with PHESGO. Among patients who tested positive to anti-trastuzumab antibodies, neutralizing anti-trastuzumab antibodies were detected in one patient treated with PHESGO.

The clinical relevance of the development of anti-pertuzumab, anti-trastuzumab or anti-recombinant human hyaluronidase PH20 antibodies after treatment with PHESGO is unknown.
6.3 Postmarketing Experience
The following adverse reactions have been identified with the use of intravenous pertuzumab and trastuzumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Glomerulopathy
- Immune thrombocytopenia
- Tumor lysis syndrome (TLS): Patients with significant tumor burden (e.g. bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

7 DRUG INTERACTIONS
Patients who receive anthracycline after stopping PHESGO may be at increased risk of cardiac dysfunction because of PHESGO’s long washout period [see Clinical Pharmacology (12.3)]. If possible, avoid anthracycline-based therapy for up to 7 months after stopping PHESGO. If anthracyclines are used, carefully monitor the patient’s cardiac function.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Pharmacovigilance Program
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.

Risk Summary
PHESGO can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of intravenous trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death (see Data). In an animal reproduction study, administration of pertuzumab to pregnant cynomolgus monkeys during the period of organogenesis resulted in oligohydramnios, delayed fetal kidney development, and embryo-fetal deaths at clinically relevant exposures that were 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C\text{max} (see Data). Apprise the patient of the potential risks to a fetus. There are clinical considerations if PHESGO is used during pregnancy or within 7 months prior to conception (see Clinical Considerations).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Monitor women who received PHESGO during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data
Human Data
In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. These case reports described oligohydramnios in pregnant women who received trastuzumab either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after trastuzumab was stopped. In one case, trastuzumab therapy resumed after amniotic index improved and oligohydramnios recurred.

**Animal Data**

PHESGO for subcutaneous injection contains pertuzumab, trastuzumab, and hyaluronidase [see Description (11)].

**Pertuzumab:**

Pregnant cynomolgus monkeys were treated on Gestational Day (GD) 19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on $C_{\text{max}}$. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85%. At Cesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights, and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

**Trastuzumab:**

In studies where intravenous trastuzumab was administered to pregnant cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

**Hyaluronidase:**

In an embryo-fetal study, mice have been dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (recombinant human) at dose levels up to 2,200,000 U/kg, which is >2,400 and 3,600, based on loading and maintenance doses, respectively, times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is >400 and 600, based on loading and maintenance doses, respectively, times higher than the human dose.

In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase (recombinant human) from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is >1,200 and 1,800, based on loading and maintenance doses, respectively, times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

**8.2 Lactation**

**Risk Summary**

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. Published data
suggest that human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the milk of lactating cynomolgus monkeys but not associated with neonatal toxicity (see Data). Consider the developmental and health benefits of breast feeding along with the mother’s clinical need for PHESGO treatment and any potential adverse effects on the breastfed child from PHESGO or from the underlying maternal condition. This consideration should also take into account the elimination half-life of pertuzumab and the trastuzumab wash out period of 7 months [see Clinical Pharmacology (12.3)].

Data
In lactating cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of maternal serum concentrations after pre- (beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (25 times the recommended weekly human dose of 2 mg/kg of intravenous trastuzumab). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

8.3 Females and Males of Reproductive Potential
PHESGO can cause embryo-fetal harm when administered during pregnancy.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to the initiation of PHESGO.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PHESGO [see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)].

8.4 Pediatric Use
The safety and effectiveness of PHESGO in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of patients in the FeDeriCa study (n=500) treated with PHESGO, 11% were 65 and over, while 1.6% were 75 and over. Clinical studies of PHESGO did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

In the intravenous trastuzumab trials, the risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients, in both those receiving treatment for adjuvant therapy or metastatic disease. Other differences in safety or effectiveness were not observed between elderly patients and younger patients. In the intravenous pertuzumab in combination with trastuzumab trials, the risk of decreased appetite, anemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral and hypomagnesemia was increased in patients 65 years of age and older compared to patients less than 65 years of age.

11 DESCRIPTION
PHESGO is a combination of pertuzumab, trastuzumab, and hyaluronidase.

Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein
(HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture. Pertuzumab has an approximate molecular weight of 148 kDa. Trastuzumab is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture. Trastuzumab has a molecular weight of approximately 148 kDa.

Hyaluronidase (recombinant human) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is a glycosylated single-chain protein produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (recombinant human) has a molecular weight of approximately 61 kDa.

PHESGO (pertuzumab, trastuzumab, and hyaluronidase-zzzf) injection is a sterile, preservative-free, clear to opalescent, and colorless to slightly brownish solution supplied in single-dose vials for subcutaneous administration.

PHESGO injection is supplied as two different configurations:

- PHESGO is supplied in a 15 mL single-dose vial containing 1,200 mg of pertuzumab, 600 mg of trastuzumab, and 30,000 units of hyaluronidase, and α,α-trehalose (397 mg), L-histidine (6.75 mg), L-histidine hydrochloric monohydrate (53.7 mg), L-methionine (22.4 mg), polysorbate 20 (6 mg), and sucrose (685 mg) with a pH of 5.5.

- PHESGO is supplied in a 10 mL single-dose vial containing 600 mg of pertuzumab, 600 mg of trastuzumab, and 20,000 units of hyaluronidase, and α,α-trehalose (397 mg), L-histidine (4.4 mg), L-histidine hydrochloric monohydrate (36.1 mg), L-methionine (14.9 mg), polysorbate 20 (4 mg), and sucrose (342 mg) with a pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2 and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signaling pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively.

Trastuzumab binds to subdomain IV of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated cell proliferation and PI3K signaling pathway in human tumor cells that overexpress HER2.

Both pertuzumab and trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) have been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models.

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase in PHESGO acts transiently and locally.
The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

Hyaluronidase has been shown to increase the absorption rate of a trastuzumab product into the systemic circulation when given in the subcutis of Göttingen Minipigs.

### 12.2 Pharmacodynamics

**Cardiac Electrophysiology**

The effect of intravenous pertuzumab with an initial dose of 840 mg followed by a maintenance dose of 420 mg every three weeks on QTc interval was evaluated in a subgroup of 20 patients with HER2-positive breast cancer (NCT00567190). No large changes in the mean QT interval (i.e., greater than 20 ms) from placebo based on Fridericia correction method were detected in the trial. A small increase in the mean QTc interval (i.e., less than 10 ms) cannot be excluded because of the limitations of the trial design.

The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.

### 12.3 Pharmacokinetics

The pharmacokinetics (PK) of pertuzumab and trastuzumab was characterized in the FeDeriCa study following subcutaneous administration of PHESGO (1200 mg pertuzumab/600 mg trastuzumab initial dose followed by 600 mg pertuzumab/600 mg trastuzumab every 3 weeks) and intravenous administration of pertuzumab and trastuzumab (840 mg pertuzumab/8 mg/kg trastuzumab initial dose followed by 420 mg pertuzumab/6 mg/kg trastuzumab every 3 weeks). The pharmacokinetic parameters of pertuzumab and trastuzumab are described in Table 5. Trastuzumab is estimated to reach concentrations that are < 1 mcg/mL by 7 months in at least 95% patients.

Pertuzumab Cycle 7 C\text{trough} (i.e., pre-dose cycle 8) showed non-inferiority 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). Trastuzumab Cycle 7 C\text{trough} showed non-inferiority of trastuzumab within PHESGO (58.7 mcg/mL) to intravenous trastuzumab (44.1 mcg/mL), with a geometric mean ratio of 1.33 (90% CI: 1.24–1.43). [see Clinical Studies (14.2)].

A population PK analysis reported that, following subcutaneous administration of PHESGO, the mean Cycle 7 C\text{max} and AUC\text{0-21} days of pertuzumab were 34% lower and 5% higher, respectively, than that following intravenous administration of pertuzumab. The mean Cycle 7 C\text{max} and AUC\text{0-21} days of trastuzumab were 31% lower and 9% higher, respectively, than that following intravenous administration of trastuzumab.

**Table 5: PK Parameters of Pertuzumab and Trastuzumab Following Subcutaneous Administration of PHESGO**

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab$^a$</th>
<th>Trastuzumab$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute Bioavailability</td>
<td>0.7 (18)</td>
<td>0.8 (13)</td>
</tr>
<tr>
<td>First-order absorption rate, ka (day(^{-1}))</td>
<td>0.4 (8) (\dagger)</td>
<td>0.4 (2.9) (\dagger)</td>
</tr>
<tr>
<td>T\text{max} (day)</td>
<td>4 (1–21) (\ddagger)</td>
<td>4 (1–22) (\ddagger)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\dagger\) Non-inferiority to intravenous.\n\(\ddagger\) Non-inferiority to intravenous.
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of Central Compartment (L)</td>
<td>2.8 (35)</td>
<td>2.9 (19)</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear Elimination Clearance (L/day)</td>
<td>0.2 (24)</td>
<td>0.1 (30)</td>
</tr>
<tr>
<td>Non-linear Elimination $V_{\text{max}}$ (mg/day)</td>
<td>N/A</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Non-linear Elimination $K_{\text{m}}$ (mg/L)</td>
<td>N/A</td>
<td>34 (39)</td>
</tr>
</tbody>
</table>

* Parameters represented as population mean (intersubject variability) unless otherwise specified
a Parameters obtained from FeDeriCa population PK model unless otherwise specified
b Parameters obtained from subcutaneous trastuzumab population PK model unless otherwise specified
† Residual standard error
‡ Median (range) values from FeDeriCa study

**Specific Populations**

Lean body weight and baseline serum albumin level were included as significant covariates in the pertuzumab population PK model. However, no dose adjustments based on body weight or baseline albumin level are needed, as the exposure changes are not considered clinically relevant.

Body weight showed a statistically significant influence on trastuzumab PK. In patients with a body weight < 58 kg, mean Cycle 7 $\text{AUC}_{0-21}$ days of trastuzumab was about 34% higher after PHESGO than after intravenous trastuzumab treatment, whereas in the highest BW group (> 77 kg) Cycle 7 $\text{AUC}_{0-21}$ days was 24% lower after PHESGO than after intravenous trastuzumab treatment. However, no body weight-based dose adjustments are needed, as the exposure changes are not considered clinically relevant.

No clinically significant differences in the pharmacokinetics of pertuzumab and trastuzumab were observed based on age (25 to 80 years), race (Asian and non-Asian) and renal impairment (creatinine clearance determined by Cockcroft-Gault 30 mL/min or greater). The effects of hepatic impairment on the pharmacokinetics of pertuzumab and trastuzumab are unknown.

**Drug Interaction Studies**

There have been no formal drug interaction studies performed with PHESGO in humans. Clinically significant interactions among pertuzumab, trastuzumab, and concomitant medications used in clinical trials have not been observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PHESGO contains pertuzumab, trastuzumab, and hyaluronidase.

**Pertuzumab**

Studies have not been performed to evaluate the carcinogenicity or mutagenic potential of pertuzumab. No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab.

No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six months duration in cynomolgus monkeys.

**Trastuzumab**

Trastuzumab has not been tested for carcinogenicity potential.

No evidence of mutagenic activity was observed when trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays at concentrations of up to 5000 mcg/mL. In an in vivo micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg of trastuzumab.
A fertility study was conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of intravenous trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

**Hyaluronidase**

Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. In addition, when subcutaneous hyaluronidase (recombinant human) was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is >223 and 335, based on loading and maintenance doses, respectively, times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

### 14 CLINICAL STUDIES

#### 14.1 Neoadjuvant and Adjuvant Treatment of Breast Cancer

The effectiveness of PHESGO for use in combination with chemotherapy has been established for the treatment of patients with HER2-positive early breast cancer. Use of PHESGO for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous pertuzumab and intravenous trastuzumab administered in combination with chemotherapy in adults with HER2-overexpressing early breast cancer (NCT00545688, NCT00976989, NCT02132949, NCT01358877) and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between PHESGO and intravenous pertuzumab and intravenous trastuzumab in FeDeriCa [see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)].

**FeDeriCa**

The FeDeriCa study (NCT03493854) was an open-label, multicenter, 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 ≥ 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/m²) and cyclophosphamide (600 mg/m²) every 2 weeks followed by paclitaxel (80 mg/m²) weekly for 12 weeks
- 4 cycles of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every 3 weeks followed by 4 cycles of docetaxel (75 mg/m² for the first cycle and then 100 mg/m² 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 according to Table 6 as follows:

**Table 6: Dosing and Administration of PHESGO, Intravenous Pertuzumab, Intravenous Trastuzumab, and Subcutaneous Trastuzumab**
<table>
<thead>
<tr>
<th>Medication</th>
<th>Administration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>PHESGO</td>
<td>Subcutaneously</td>
<td>1200 mg/600 mg</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Intravenously</td>
<td>840 mg</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Intravenously</td>
<td>8 mg/kg</td>
</tr>
<tr>
<td>Trastuzumab-oysk</td>
<td>Subcutaneously</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

* In adjuvant period substitution of intravenous trastuzumab for subcutaneous trastuzumab was permitted at investigator discretion

FeDeriCa was designed to demonstrate non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) pertuzumab serum $C_{\text{trough}}$ from PHESGO pertuzumab to the intravenous pertuzumab (primary endpoint) [see Clinical Pharmacology 12.3]. Secondary endpoints included Cycle 7 serum $C_{\text{trough}}$, 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 (range: 25-81), and the majority of patients were White (66%). The majority of patients had hormone receptor-positive disease (61%) or node-positive disease (58%).

The pCR rate was 59.7% (95% CI: 53.3, 65.8) in the PHESGO arm and 59.5% (95% CI: 53.2, 65.6) in the intravenous pertuzumab and trastuzumab arm.

| Table 7: Summary of Pathological Complete Response (pCR) (FeDeriCa) |
|---------------------------------|-------------------|
|                                 | PHESGO n=248      | Intravenous pertuzumab + trastuzumab n=252 |
| pCR (ypT0/is, ypN0)             | 148 (59.7%)       | 150 (59.5%) |
| Exact 95% CI for pCR Rate       | (53.3%, 65.8%)    | (53.2%, 65.6%) |
| Difference in pCR rate (SC minus IV arm) | 0.15%            | (-8.7%; 9.0%) |

1 Confidence interval for one sample binomial using Pearson-Clopper method
2 Hauck-Anderson continuity correction has been used in this calculation

14.2 Metastatic Breast Cancer

The effectiveness of PHESGO for use in combination with docetaxel has been established for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Use of PHESGO for this indication is supported by evidence from adequate and well-controlled studies conducted with intravenous pertuzumab and intravenous trastuzumab administered in combination with chemotherapy in adults with HER2-overexpressing metastatic breast cancer (NCT00567190) and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between PHESGO and intravenous pertuzumab and intravenous trastuzumab in FeDeriCa [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)].

14.3 Patient Experience

The PHranceSCa study (NCT03674112) was 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. After Cycle 6, 136 out of 160 patients (85%) reported preferring subcutaneous administration of PHESGO over intravenous pertuzumab and trastuzumab and the most common reason was that administration required less time in the clinic. After Cycle 6, 22 out of 160 patients (14%) reported preferring intravenous pertuzumab and trastuzumab over PHESGO and the most common reason was feels more comfortable during administration. Two out of 160 patients (1%) had no preference for the route of administration. All 160 patients (100%) completed the preference questionnaire.

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
PHESGO (pertuzumab, trastuzumab, and hyaluronidase-zzxf) injection is a sterile, preservative-free, clear to opalescent, and colorless to slightly brownish solution in single-dose vials for subcutaneous administration supplied as each carton containing one single-dose vial:

- 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase/15 mL (80 mg, 40 mg, and 2,000 units/mL) (NDC 50242-245-01).
- 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase/10 mL (60 mg, 60 mg, 2,000 units/mL) (NDC 50242-260-01).

16.2 Storage and Handling
Store PHESGO 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.

17 PATIENT COUNSELING INFORMATION
Cardiomyopathy

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [see Warnings and Precautions (5.1)].

Embryo-Fetal Toxicity

- 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 female patients to contact their healthcare provider with a known or suspected pregnancy [see Use in Specific Populations (8.1)].

- Advise women who are exposed to PHESGO during pregnancy or within 7 months prior to conception that there is a pregnancy pharmacovigilance program that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Genentech [see Use in Specific Populations (8.1)].

- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PHESGO [see Use in Specific Populations (8.3)].

Hypersensitivity and Administration-Related Reactions

- Advise patients to contact their healthcare provider immediately and to report any symptoms of hypersensitivity and administration-related reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, urticaria, angioedema, breathing problems, or chest pain [see Warnings and Precautions (5.5)].
Manufactured by:

**Genentech, Inc.**
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

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