PHESGO™

PERTUZUMAB-TRASTUZUMAB

PHESGO®
(pertuzumab-trastuzumab fixed-dose combination for subcutaneous injection)

PLUS CHEMOTHERAPY FOR THE **NEOADJUVANT AND ADJUVANT TREATMENT OF HER2-POSITIVE EARLY BREAST CANCER (eBC)** AND FOR THE **FIRST-LINE TREATMENT OF HER2-POSITIVE METASTATIC BREAST CANCER (mBC)**

PRODUCT MONOGRAPH

M-AE-00000086

TABLE OF CONTENTS

Pertuzumab-trastuzumab fixed-dose combination for subcutaneous (SC) injection

1. HER2 POSITIVE DISEASE BURDEN

1.1. Epidemiology of breast cancer (BC)

Global prevalence[1]

- BC is the **most frequently** diagnosed cancer
- It is a leading cause of cancer related deaths in **women worldwide**
- Estimated number of new BC cases **2.08 million in 2018** (25% of all cancers in women)
- Global BC deaths approximately **626,679**

Prevalence of HER2-positive BC in the population[2,3]

15–20% of primary BC

23.5% of BC in the Asian population

HER2-positive BC mortality rate according to Surveillance, Epidemiology, and End Results Program (SEER) data 2015[4-6]

78,000–104,000 deaths per year globally[4-6]

1.2. Disease burden of BC

Impact of BC on patients

- Compared to the general population, patients with BC experience:

- Reduced health related quality of life (HRQoL)[7,8]
- Fatigue[9-13]
- Sexual dysfunction[9-13]
- Infertility[9-13]
- Stress[11,14]
- Mental disorders[11,14]

Disease recurrence

- Suboptimal treatment of early stage BC (eBC) increases the risk of disease recurrence[15,16]
- Natural life expectancy for women in high-income countries is >80 years[15,16]
- Recurrent BC is responsible for up to two decades median loss of life-years per patient[15,16]
- BC recurrence is associated with frequent hospital visits and interventions, impacting patient HRQoL[17]
- Nearly 90% of patients with metastatic BC (mBC) will be admitted to hospital, typically two to four times[17]

1.3. Economic burden of BC

Direct and indirect costs associated with BC

Belgium study conclusion[18]

- Productivity loss from BC accounted for 89% of the total costs
- Direct costs accounted for 11% of the total costs
- The discounted annual healthcare costs over 6 years were estimated to be greater for patients with mBC compared to those with eBC

US study conclusion

- Patients with early-stage disease tend to incur lower expenditures than patients with metastatic presentation[19]
- Among the treatment-related costs in the first 12 months after diagnosis, chemotherapy accounted for the highest percentage to the total claim costs for Stage IV disease, almost three times higher than in Stage I/II BC[19]
- Costs of care were approximately double for patients with BC diagnosed with distant versus local disease, both in the initial and the last year of life phases
- Treating advanced versus eBC is associated with significant increases in incremental costs in the US[19]

Australian study conclusion

- Indirect costs made up 62% of total BC costs[20]

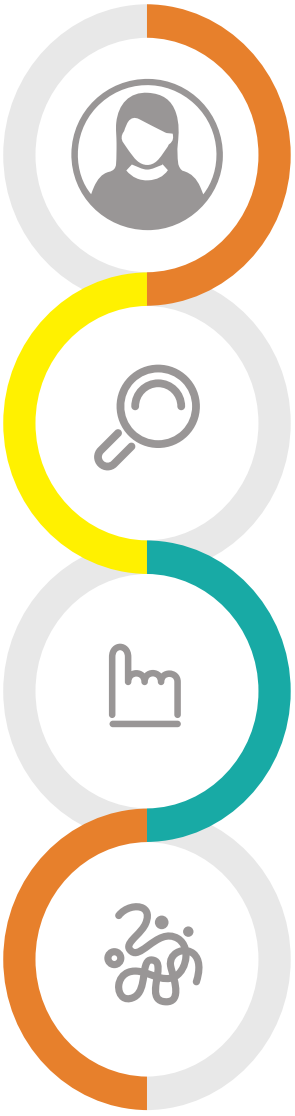
Swedish study conclusion

- Indirect costs constituted 70% of total costs[21]

Burden associated with BC recurrence

- Patients with eBC who experienced recurrence
  - required more costly care than patients who did not develop recurrent disease[22,23]
- Contralateral and locoregional events
  - they are associated with high costs of further surgery and/or radical radiotherapy[24]
  - a high proportion of patients go on to experience distant recurrence within 5 years[24]
  - this incurs the additional costs of treating metastatic disease[24]

Productivity losses due to BC

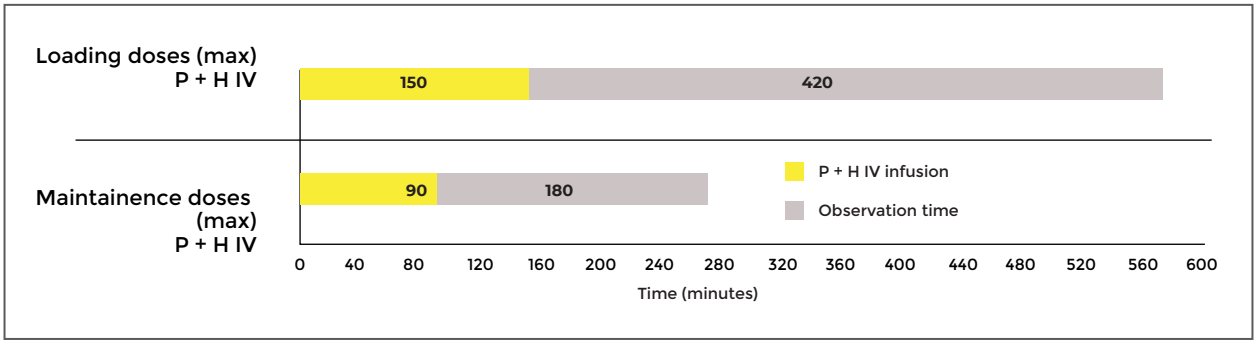


- BC represents the greatest productivity loss among all cancers in the female population[25]
  - the incidence of BC is at its peak during mid-working age in the working-age population[25]
  - it is the most common and fastest growing cancer[25]
- BC progression leads to
  - diminished likelihood of employment[26]
  - increased workplace hours missed[26]
  - increased cost burden[26]
- BC workers experience a great influence of the side effects of anticancer drugs on
  - quality of life[27]
  - absenteeism[27]
  - presenteeism[27]
- There is substantial loss of productivity in patients with mBC compared with patients living with non-metastatic disease[26,27]

2. UNMET MEDICAL NEED IN HER2-POSITIVE BC

2.1. Intravenous (IV) HER2+ cancer care offers the results patients need - but at what costs?

- Treatment with IV PERJETA® (P)+ Herceptin® (H) has proven benefits in HER2+ BC, for adjuvant, neoadjuvant and metastatic settings.[28-34]
- However, many patients still receive this dual HER2-blockade via IV, requiring up to **9.5 hours - an entire day** - of patient and staff time to be spent in the IV suite.[35,36]



- **IV preparation** can also take up to **22 minutes** per treatment given, potentially occupying pharmacy staff for almost **45 minutes** per dual blockade session.[37]
- These demands on time and resources impact not only treatment capacity but also staff wellbeing, with high workload cited as a major cause of stress and poor mental health.[37]

2.2. IV HER2+ cancer care is effective but time-consuming

- Every appointment for IV HER2+ cancer care can require up to **40 minutes** of active **HCP time** involving oncologists, nurses, pharmacists and pharmacy staff.[37]
- **Drug preparation** can account for up to **50%** of this time, almost as much as drug initiation and observation combined.[37]

Active HCP time in the treatment room and drug preparation area per session[37]

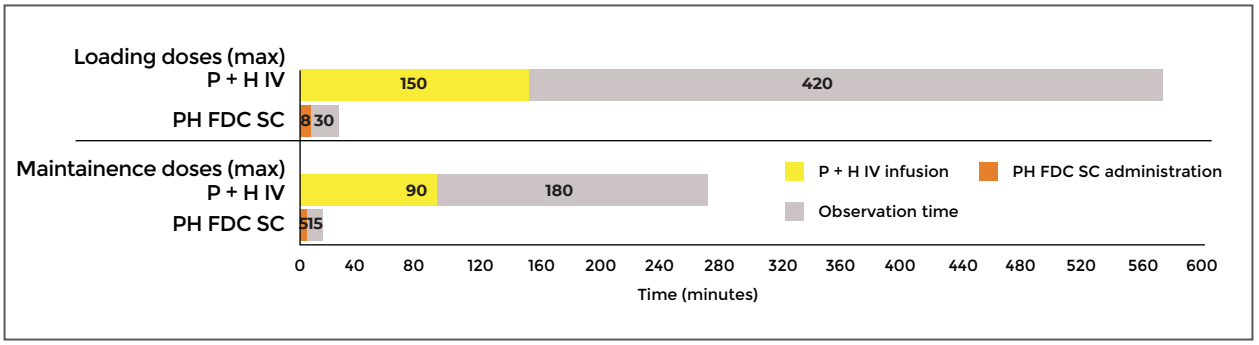
13.9 minutes Observed time in drug preparation area

17.9 minutes Observed time in treatment room

2.3. Fixed-dose SC combination of trastuzumab and pertuzumab: A new way to approach HER2 + breast cancer treatment

- Giving you the benefits of PERJETA® and Herceptin® in one ready-to-use, fixed-dose treatment for SC injection.[35,36,38,39]

Administration in minutes, not hours[35,36,39]



2.4. Liberating staff to use their time as they choose

- Based on experience with trastuzumab SC, using SC formulations can free up as much as **70%** of active HCP time.[37,40-42]

Time savings were projected at an average of **5 hours** per patient per treatment course, potentially increase when two treatments are given together[37]

How much time saved could that mean for your centre?

- In the PHranceSCa study, HCPs saw potential benefits of fixed-dose SC combination of trastuzumab and pertuzumab with respect to staff time and efficiency across all stages of care.[43]

77% agreed that it results in less drug wastage when using FDC

95% agreed SC administration takes least time from start to finish vs IV

79% agreed fixed-dose SC combination of trastuzumab and pertuzumab was the best option for optimising patient care within their treatment site

2.5. Releasing resources and budget for your entire centre

- Based on experience with trastuzumab SC, using SC formulations could **reduce IV infusion chair times** for patients by as much as **90%**.[37,40-42]
- Shorter chair times are expected to improve patient throughput, allowing greater patient access and shortening waiting lists.[37,39]
- Other perceived benefits of fixed-dose SC combination include:

01 Less resource use for administration[43]

02 Reduced costs due to lost staff productivity[41]

03 Less drug wastage[43]

04 Reduced costs for IV preparation times[43]

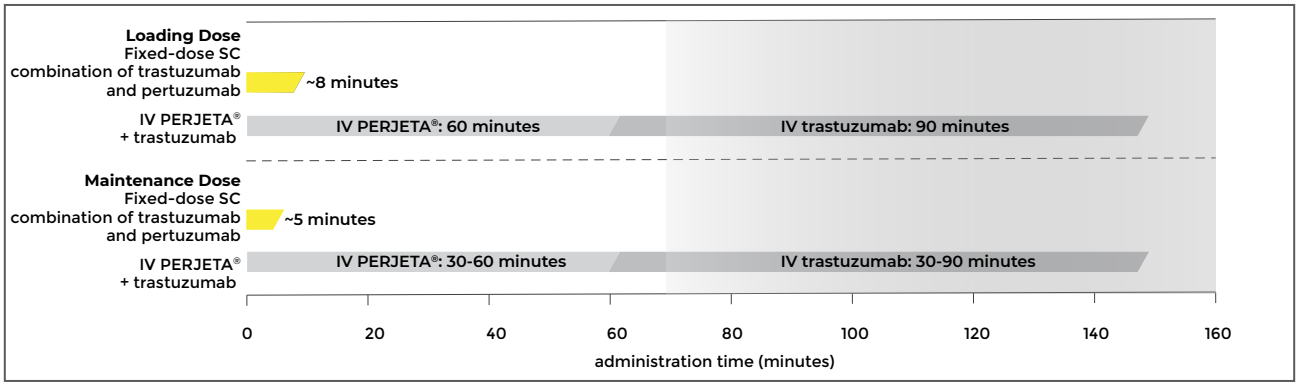
05 More efficient use of storage space[43]

3. COMBINING THE ANTIBODIES YOU KNOW IN ONE FASTER MODE OF ADMINISTRATION

Pertuzumab and trastuzumab are recombinant humanized IgG1κ monoclonal antibodies, which target HER2, a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab and trastuzumab bind to distinct HER2 epitopes without competing and have complementary mechanisms for disrupting HER2 signaling, resulting in augmented anti-proliferative activity when given in combination.[35,36]

The fixed-dose SC combination of trastuzumab and pertuzumab is a faster treatment option for your patients and practice.[35,39]

Faster administration with fixed-dose subcutaneous combination of trastuzumab and pertuzumab vs IV PERJETA® + trastuzumab*[35,39]



Fixed-dose SC combination of trastuzumab and pertuzumab requires[39]:

NO reconstitution • **NO** dilution • **NO** weight adjustments

NO IV loading dose • **NO** port access with a SC injection

Patients currently receiving IV PERJETA® + trastuzumab can be transitioned to fixed-dose SC combination of trastuzumab and pertuzumab if eligible.[39]

*Refers to actual injection time of fixed-dose SC combination of trastuzumab and pertuzumab vs infusion time of IV PERJETA® + trastuzumab 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. Please see the PERJETA® full Prescribing Information for additional dosing information for PERJETA® + trastuzumab.

The same treatment schedule you are used to with PERJETA® + trastuzumab-based therapy

In eBC

- Eligible patients should receive fixed-dose SC combination of trastuzumab and pertuzumab as part of a complete treatment regimen, every 3 weeks for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first† [35,39]

In mBC

- Eligible patients should receive fixed-dose SC combination of trastuzumab and pertuzumab alongside docetaxel as first-line treatment, every 3 weeks until disease progression or unmanageable toxicity, whichever occurs first.[35,39]
- The same treatment schedule you are used to with PERJETA® + trastuzumab-based therapy.[35,39]

†In eBC, patients who begin fixed-dose SC combination of trastuzumab and pertuzumab in the neoadjuvant setting should receive 3-6 cycles before surgery and should continue treatment after surgery, every 3 weeks, to complete 1 year (up to 18 cycles). Patients who begin treatment in the adjuvant setting should receive a total of 1 year (up to 18 cycles) of fixed-dose SC combination of trastuzumab and pertuzumab, every 3 weeks, starting on Day 1 of the first taxane-containing cycle.

4. TARGET POPULATION FOR FIXED-DOSE SC COMBINATION OF TRASTUZUMAB AND PERTUZUMAB

The target populations of fixed-dose SC combination of trastuzumab and pertuzumab are the same as defined for PERJETA®- Herceptin® in combination with chemotherapy in HER2-positive BC and are therefore the same as per the PERJETA® label.[35,39]

01 Neoadjuvant treatment of HER2-positive eBC patients at high-risk of recurrence (i.e. lymph node-positive or a tumor size of >2 cm).[35,39]

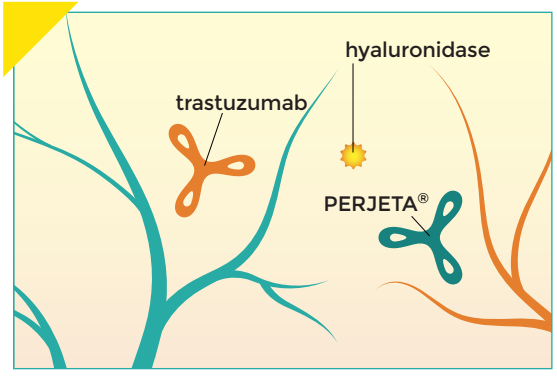
02 Adjuvant treatment of HER2-positive eBC patients at high-risk of recurrence (at minimum lymph node-positive patients regardless of HR status) without prior neoadjuvant treatment.[35,39]

03 Adjuvant treatment following neoadjuvant treatment of HER2-positive eBC patients who achieved pathological complete response (i.e. neoadjuvant treatment continuation).[35,39]

04 First-line treatment of HER2-positive mBC patients.[35,39]

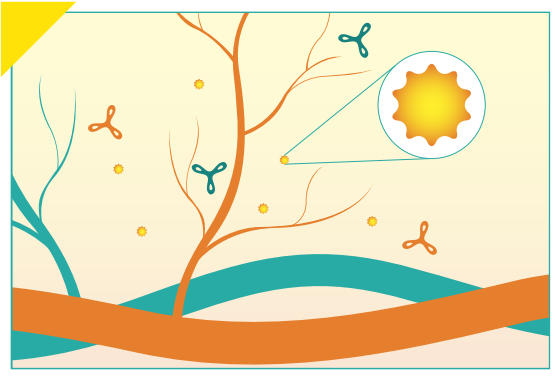
5. PROPOSED MECHANISM OF ACTION FOR THE FIXED-DOSE SC COMBINATION OF TRASTUZUMAB AND PERTUZUMAB

5.1. Specially formulated with hyaluronidase[39,44,45]



Fixed-dose SC combination of trastuzumab and pertuzumab includes 2 monoclonal antibodies, with recombinant human hyaluronidase.

Fixed-dose SC combination of trastuzumab and pertuzumab is designed to work with trastuzumab for a dual-HER2 blockade. In preclinical models, PERJETA® targeted a different subdomain on the HER2 receptor than trastuzumab, to block dimerization with HER1, HER3, and HER4 receptors and provide a dual blockade of HER2-driven signaling pathways.



Hyaluronidase is used to deliver pertuzumab and trastuzumab subcutaneously.

Hyaluronidase allows SC delivery of higher drug volumes.

Hyaluronidase is an endoglycosidase used to increase dispersion and absorption of co-administered drugs when administered subcutaneously.

5.2. How hyaluronidase is thought to work?[39]

Hyaluronidase increases permeability of the SC tissue by depolymerizing hyaluronan, based on preclinical studies.

In the doses administered, hyaluronidase in the fixed-dose SC combination of trastuzumab and pertuzumab acts transiently and locally.

The effects of hyaluronidase are reversible, and permeability of the SC 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, based on animal studies.

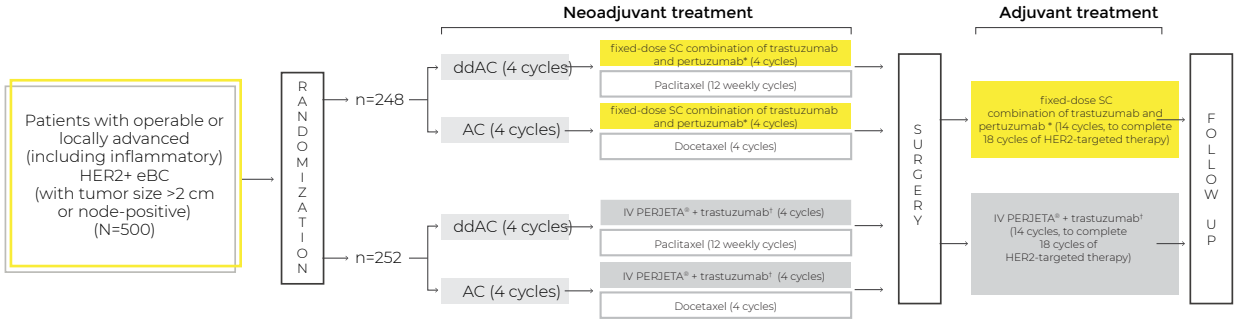
6. FIXED-DOSE SC COMBINATION OF TRASTUZUMAB AND PERTUZUMAB: CLINICAL EFFICACY AND SAFETY

6.1. FeDeriCa

FeDeriCa evaluated the pharmacokinetics (PK), efficacy, and safety of fixed-dose SC combination of trastuzumab and pertuzumab vs IV pertuzumab + trastuzumab.

Study design[39,46,47]

Phase III, randomized, open-label trial designed to demonstrate non-inferiority of fixed-dose SC combination of trastuzumab and pertuzumab compared to IV PERJETA® and trastuzumab.



Treatment cycles with fixed-dose SC combination of trastuzumab and pertuzumab or IV PERJETA® + trastuzumab were received every 3 weeks.
Patients received adjuvant radiotherapy and endocrine therapy as per investigator's discretion.

Primary endpoint

Non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) pertuzumab serum Ctrough.

Secondary endpoints

Non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) trastuzumab Ctrough, efficacy (pCR),‡ and safety.

Stratification factors

Hormone receptor status; clinical stage at presentation (Stage II-IIIA or IIIB-IIIC); type of chemotherapy.

***Fixed-dose SC combination of trastuzumab and pertuzumab dosing:** 1200 mg pertuzumab/600 mg trastuzumab/30,000 units hyaluronidase loading dose, followed by 600 mg pertuzumab/600 mg trastuzumab/20,000 units hyaluronidase maintenance dose.
†**IV PERJETA® dosing:** 840 mg loading dose, 420 mg for subsequent cycles; IV trastuzumab dosing: 8 mg/kg loading dose, 6 mg/kg for subsequent cycles. In adjuvant period, substitution of IV trastuzumab for SC trastuzumab (trastuzumab-oysk) was permitted at investigator discretion. Trastuzumab-oysk was given as a fixed dose of 600 mg. 61 patients received trastuzumab-oysk.
‡pCR=pathological complete response (ypT0/is, ypN0, defined as the absence of invasive neoplastic cells in the breast and in the axillary lymph nodes).
Chemotherapy regimens: ddAC dosing: doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks; **AC dosing:** doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks; **paclitaxel dosing:** 80 mg/m^2 weekly; **docetaxel dosing:** 75 mg/m^2 every 3 weeks. Docetaxel dose could be escalated to 100 mg/m^2 at subsequent cycles at investigator's discretion.
AC=doxorubicin + cyclophosphamide; ddAC=dose-dense doxorubicin-cyclophosphamide.

Fixed-dose SC combination of trastuzumab and pertuzumab demonstrated non-inferior PK vs IV pertuzumab + trastuzumab.[39,46]

PK results for fixed-dose SC combination of trastuzumab and pertuzumab vs IV pertuzumab and trastuzumab[39,46]

	Fixed-dose SC combination of trastuzumab and pertuzumab (n=206)	IV PERJETA® + trastuzumab (n=203)
Primary endpoint: pertuzumab Cycle 7 C_{trough}	88.7 mcg/mL	72.4 mcg/mL
Geometric mean ratio	1.22 (90% CI: 1.14-1.31)	
Secondary endpoint: trastuzumab Cycle 7 C_{trough}	58.7 mcg/mL	44.1 mcg/mL
Geometric mean ratio	1.33 (90% CI: 1.24-1.43)	

· Non-inferiority was concluded if the lower bound of the 90% confidence interval of the geometric mean ratio was ≥0.8

Secondary endpoint: efficacy (pCR)*[39,46]

Fixed-dose SC combination of trastuzumab and pertuzumab (n=248)	IV PERJETA® + trastuzumab (n=252)
59.7% (95% CI: 53.3-65.8)	59.5% (95% CI: 53.2-65.6)

*pCR=pathological complete response (ypT0/is, ypN0, defined as the absence of invasive neoplastic cells in the breast and in the axillary lymph nodes).

Summary of adverse reactions (ARs) occurring in ≥15% of patients who received the fixed-dose SC combination of trastuzumab and pertuzumab[39,46]

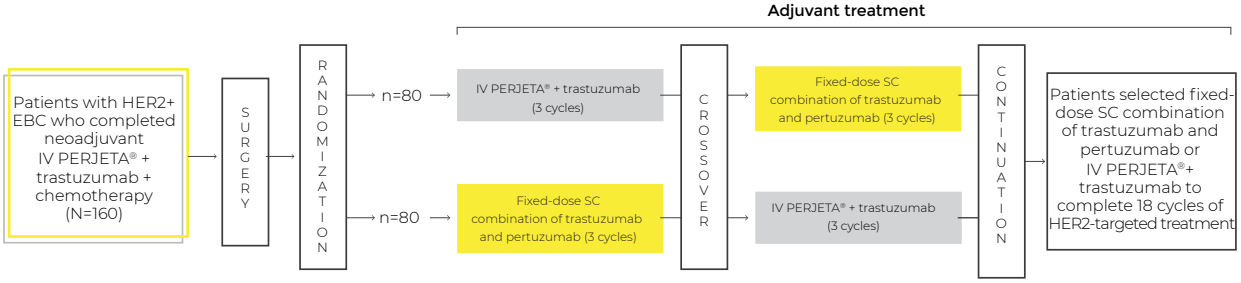
	All Grades (%)		Grades 3-4 (%)	
	Fixed-dose SC combination of trastuzumab and pertuzumab (n=248)	IV PERJETA® (pertuzumab) + IV/SC trastuzumab (n=252)	Fixed-dose SC combination of trastuzumab and pertuzumab (n=248)	IV PERJETA® + IV/SC trastuzumab (n=252)
Rash	16	21	0.4	0
Dry skin	15	13	0.4	0
Mucosal inflammation	15	20	0.8	1.2
Injection site reaction*	15	0.8	0	0
Cough	15	13	0.4	0

*An injection site reaction was defined as a local reaction.

6.2. PHranceSCa

Study design[39,48,49]

Phase II, randomized, open-label, crossover trial of patients with HER2+ eBC. The primary objective of the study was to evaluate patient preference for fixed-dose SC combination of trastuzumab and pertuzumab.

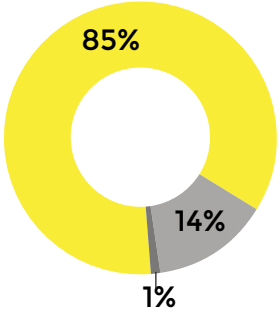


Primary endpoint

Percentage of patients who preferred fixed-dose SC combination of trastuzumab and pertuzumab over IV PERJETA® + trastuzumab when surveyed after Cycle 6 of adjuvant treatment.[39,49]

Treatment that helps patients feel less like patients

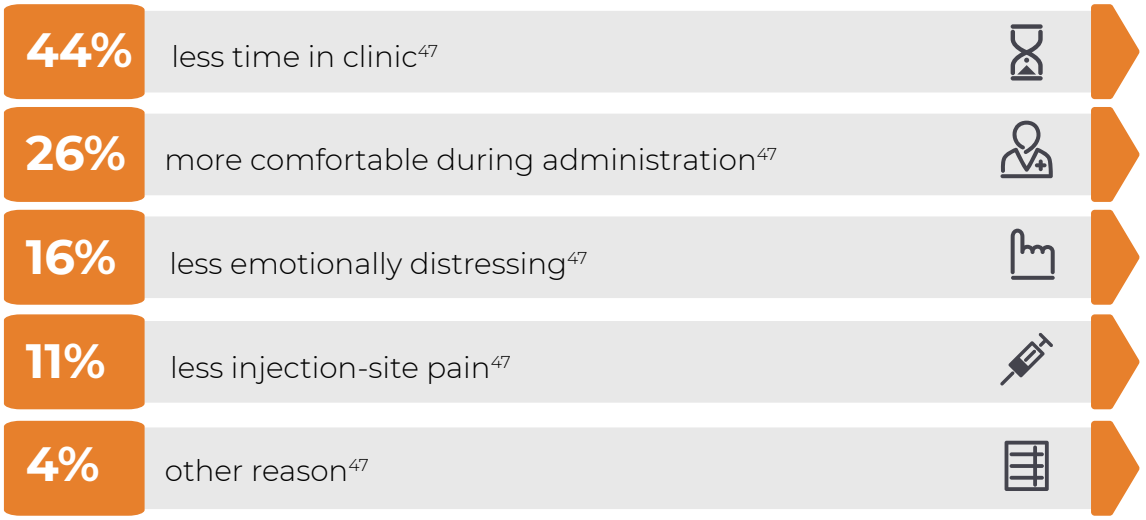
- In the PHranceSCa study, 85% percent of patients preferred fixed-dose SC combination of trastuzumab and pertuzumab over IV pertuzumab + trastuzumab.[39]



- **Preferred fixed-dose SC combination of trastuzumab and pertuzumab** (n=136/160)
- **Preferred IV PERJETA® + trastuzumab** (n=22/160)
- **No preference** (n=2/160)

- 14% of patients preferred using IV PERJETA® + trastuzumab, citing more comfort during administration as the most common reason.[39,49]

- Main reasons for fixed-dose SC combination of trastuzumab and pertuzumab preference were **'less time in clinic'** and **'more comfortable during administration'**, consistent with IV pertuzumab + trastuzumab.[43,50]



- Most patients (87%) chose fixed-dose SC combination of trastuzumab and pertuzumab to complete their treatment.[50]

Safety data based on interim analysis[47,48]

	IV PERJETA® (pertuzumab) + trastuzumab →	Fixed-dose SC combination of trastuzumab and pertuzumab	Fixed-dose SC combination of trastuzumab and pertuzumab →	IV PERJETA® + trastuzumab	
Patients with ≥1 of the following: n (%)	Cycles 1-3 (n=56)	Cycles 4-6 (n=33)	Cycles 1-3 (n=60)	Cycles 4-6 (n=32)	Total patients (n=116)
ARs	35 (63%)	22 (67%)	35 (58%)	14 (44%)	80 (69%)
Most common ARs (>5% of patients)					
Local injection-site reaction	0	6 (18%)	15 (25%)	0	21 (18%)
Radiation skin injury	11 (20%)	2 (6%)	6 (10%)	5 (16%)	24 (21%)
Diarrhea	9 (16%)	5 (15%)	4 (7%)	0	15 (13%)
Hot flush	3 (5%)	2 (6%)	2 (3%)	0	7 (6%)
Systemic infusion reaction	3 (5%)	0	0	0	3 (3%)
Systemic injection reaction	0	1 (3%)	1 (2%)	0	2 (2%)

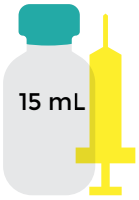
7. RECOMMENDED DOSING AND ADMINISTRATION FOR FIXED-DOSE SC COMBINATION OF TRASTUZUMAB AND PERTUZUMAB

7.1. Dosing and administration for fixed-dose SC combination of trastuzumab and pertuzumab

Fixed-dose SC combination of trastuzumab and pertuzumab has different dosage and administration instructions than IV pertuzumab, IV trastuzumab, and SC trastuzumab when administered alone. Do not substitute fixed-dose SC combination of trastuzumab and pertuzumab for or with PERJETA®, trastuzumab, ado-trastuzumab emtansine (KADCYLA®), or fam-trastuzumab deruxtecan.[39]

Fixed-dose SC combination of trastuzumab and pertuzumab should be administered every 3 weeks[39]

Loading (initial) dose

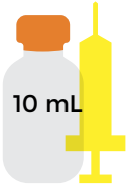


1200 mg pertuzumab, 600 mg trastuzumab, 30,000 units hyaluronidase per 15 mL supplied in a **single-dose, ready-to-use vial**

Administer subcutaneously over approximately **8 minutes**

Observe for hypersensitivity or administration-related reactions: minimum of **30 minutes***

Maintenance dose



600 mg pertuzumab, 600 mg trastuzumab, 20,000 units hyaluronidase per 10 mL supplied in a **single-dose, ready-to-use vial**

Administer subcutaneously over approximately **5 minutes**

Observe for hypersensitivity or administration-related reactions: minimum of **15 minutes***

*Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Administration instructions[39]

Fixed-dose SC combination of trastuzumab and pertuzumab must always be administered by a healthcare professional. Fixed-dose SC combination of trastuzumab and pertuzumab is for SC use **ONLY in the thigh.**

Do NOT administer intravenously.

- Do not split the dose between 2 syringes or between 2 sites of administration.
- Injection site should be alternated between the left and right thigh only.

- New injections should be given at least 1 inch from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard.
- During the treatment course with fixed-dose SC combination of trastuzumab and pertuzumab, other SC medications should preferably be injected at different sites.

Patients currently receiving IV PERJETA® + trastuzumab can be transitioned to fixed-dose SC combination of trastuzumab and pertuzumab if eligible.

7.2. Additional dosing considerations and dose modifications

Dose sequencing[39]

- In patients receiving an anthracycline-based regimen for eBC, administer fixed-dose SC combination of trastuzumab and pertuzumab following completion of the anthracycline.
- In patients receiving fixed-dose SC combination of trastuzumab and pertuzumab for eBC with docetaxel or paclitaxel, administer docetaxel or paclitaxel after fixed-dose SC combination of trastuzumab and pertuzumab.
- In patients receiving fixed-dose SC combination of trastuzumab and pertuzumab for mBC with docetaxel, administer docetaxel after fixed-dose SC combination of trastuzumab and pertuzumab.

Transitioning from IV PERJETA® (pertuzumab) + trastuzumab to fixed-dose SC combination of trastuzumab and pertuzumab[39]

In patients receiving IV PERJETA® + trastuzumab with **<6 weeks** since their last dose → **Administer** → Fixed-dose SC combination of trastuzumab and pertuzumab as a **maintenance dose** of 600 mg, 600 mg, 20,000 units/10 mL and every **3 weeks** for subsequent administrations

In patients receiving IV PERJETA® + trastuzumab with **≥6 weeks** since their last dose → **Administer** → Fixed-dose SC combination of trastuzumab and pertuzumab as an **initial dose** of 1,200 mg, 600 mg, 30,000 units/15 mL, followed by a maintenance dose of 600 mg, 600 mg, 20,000 units/10 mL every **3 weeks** for subsequent administrations

Delayed or missed doses of fixed-dose SC combination of trastuzumab and pertuzumab[39]

If the time between 2 sequential injections is **<6 weeks**

→ **Do not wait** until the next planned dose Administer the **maintenance dose** of 600 mg, 600 mg, 20,000 units/10 mL

If the time between 2 sequential injections is **≥6 weeks**

→ **Re administer** the **initial dose** of 1,200 mg, 600 mg, 30,000 units/15 mL followed every 3 weeks thereafter by maintenance dose of 600 mg, 600 mg, 20,000 units/10 mL

Dosing adjustments[39]

- No dose adjustments for fixed-dose SC combination of trastuzumab and pertuzumab are required for patient body weight or for concomitant chemotherapy regimen.
- For chemotherapy dose modification, see relevant prescribing information.
- If patient experiences a significant injection-related reaction, slow down or pause the injection, do not move the needle out of the injection site and administer appropriate medical therapies. Evaluate and carefully monitor patients until complete resolution of signs and symptoms.
- If patient experiences a serious hypersensitivity reaction (e.g., anaphylaxis), discontinue injection immediately.

Dose modification and monitoring for left ventricular dysfunction[39]

Assess left ventricular ejection fraction (LVEF) prior to initiation of fixed-dose SC combination of trastuzumab and pertuzumab and at regular intervals during treatment.

Pre-treatment LVEF:		Withhold fixed-dose SC combination of trastuzumab and pertuzumab for at least 3 weeks for an LVEF decrease to:		Resume fixed-dose SC combination of trastuzumab and pertuzumab after 3 weeks if LVEF has recovered to:	
				Either	
eBC	≥ 55%*	<50% with a fall of ≥10%-points below pre-treatment value		≥50%	<10% points below pre-treatment value
				Either	
mBC	≥ 50%	<40%	40%-45% with a fall of ≥10%-points below pre-treatment value	>45%	40%-45% with a fall of <10%-points below pre-treatment value

* For patients receiving anthracycline-based chemotherapy, an LVEF of ≥50% is required after completion of anthracyclines before starting fixed-dose subcutaneous combination of trastuzumab and pertuzumab.

Monitor LVEF prior to initiation and then every ~12 weeks in mBC and eBC (once during neoadjuvant therapy).

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 fixed-dose SC combination of trastuzumab and pertuzumab.

7.3. Preparation and storage

Vial storage[39]

Fixed-dose SC combination of trastuzumab and pertuzumab is supplied in sterile, preservative-free, single-dose vials for SC administration. Store fixed-dose SC combination of trastuzumab and pertuzumab vials in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light, until time of use. Do not freeze.

Checking the vial[39]

- To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is fixed-dose SC combination of trastuzumab and pertuzumab and not IV PERJETA®, or IV or SC trastuzumab.
- Inspect the vial for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vial if particulates or discoloration is present. The solution should be clear to opalescent, colorless to slightly brownish. Do not shake.

Preparing the injection[39]

- A syringe, a transfer needle, and an injection needle are needed to withdraw fixed-dose SC combination of trastuzumab and pertuzumab solution from the vial and inject it subcutaneously. Fixed-dose SC combination of trastuzumab and pertuzumab is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride, and fluorinated ethylene polypropylene.
- Do not dilute fixed-dose SC combination of trastuzumab and pertuzumab. Use a syringe with a transfer needle to withdraw the fixed-dose SC combination of trastuzumab and pertuzumab solution from the vial. Discard any unused portion remaining in the vial. Remove transfer needle.
- Immediately prior to administration, attach a 25G-27G (3/8”–5/8”) hypodermic injection needle to the syringe. Check the syringe to ensure the right dose is being administered: initial dose (15 mL) or maintenance dose (10 mL).
- Inject fixed-dose SC combination of trastuzumab and pertuzumab into patient’s thigh slowly and gently over about 8 minutes for the initial dose and about 5 minutes for the maintenance dose.

Syringe storage[39]

If the syringe containing fixed-dose SC combination of trastuzumab and pertuzumab is not used immediately, it can be stored in the refrigerator for up to 24 hours (2°C to 8°C, 36°F to 46°F) and at room temperature for up to 4 hours (20°C to 25°C, 68°F to 77°F). Avoid unnecessary storage.

- If the dose is not to be administered immediately, and the solution of fixed-dose SC combination of trastuzumab and pertuzumab has been withdrawn from the vial into the syringe, replace the transfer needle with a syringe closing cap.
- Do not attach a hypodermic needle until time of administration to avoid needle clogging.
- Label the syringe with the peel-off sticker.

7.4. Treatment regimens for eBC and mBC, based on pertuzumab studies and FeDeriCa

eBC treatment regimen[35,39]

Eligible patients with HER2+ eBC should receive fixed-dose SC combination of trastuzumab and pertuzumab every 3 weeks to complete 1 year of treatment (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete treatment regimen including anthracycline- and/or taxane-based chemotherapy.

Neoadjuvant chemotherapy regimens

Neoadjuvant Setting		Adjuvant Setting
4 cycles of **fixed-dose SC combination of trastuzumab and pertuzumab** + docetaxel* (based on pertuzumab studies)	S U R G E R Y	**3 postoperative cycles** of FEC† and continue **fixed-dose SC combination of trastuzumab and pertuzumab** to complete 1 year (up to 18 cycles) of treatment ***per full Prescribing Information***
3 or 4 cycles of FEC,† followed by **3 or 4 cycles** of **fixed-dose SC combination of trastuzumab and pertuzumab** + docetaxel* (based on pertuzumab studies)		
6 cycles of **fixed-dose SC combination of trastuzumab and pertuzumab** + docetaxel* + carboplatin‡ (based on pertuzumab studies)		Continue **fixed-dose SC combination of trastuzumab and pertuzumab** to complete 1 year (up to 18 cycles) of treatment ***per full Prescribing Information***
4 cycles of ddAC,§ followed by **4 cycles** of **fixed-dose SC combination of trastuzumab and pertuzumab** + paclitaxel‖ or docetaxel* (based on a pertuzumab study and FeDeriCa)		
4 cycles of AC,¶ followed by **4 cycles** of **fixed-dose SC combination of trastuzumab and pertuzumab** + docetaxel* (based on FeDeriCa)		

Adjuvant chemotherapy regimens

Fixed-dose SC combination of trastuzumab and pertuzumab should start on Day 1 of the first taxane-containing cycle.

Non-anthracycline-based chemotherapy regimen

- 6 cycles of docetaxel** + carboplatin††

Anthracycline-based regimens

- 3 or 4 cycles of FEC‡‡ or FAC§§, followed by 3 or 4 cycles of docetaxel** or 12 cycles of weekly paclitaxel‖‖
- 4 cycles of AC¶¶ or EC***, followed by 3 or 4 cycles of docetaxel** or 12 cycles of weekly paclitaxel‖‖

*Docetaxel dosing: 75 mg/m², which could be escalated to 100 mg/m² if initial dose was well tolerated (escalation of docetaxel above 75 mg/m² is not recommended when administered with carboplatin as in TRYPHAENA [NCT00976989]).
†FEC dosing in NeoSphere (NCT00545688): 5-fluorouracil (600 mg/m²), epirubicin (90 mg/m²), and cyclophosphamide (600 mg/m²); FEC dosing in TRYPHAENA and BERENICE (NCT02132949): 5-fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (600 mg/m²).
‡Carboplatin dosing: AUC 6.
§ddAC dosing: doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every 2 weeks for 4 cycles with GCSF support.
‖Paclitaxel dosing: 80 mg/m².
¶AC dosing: 4 cycles of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every 3 weeks.
**Docetaxel dosing: 75 mg/m², which could be escalated to 100 mg/m² if initial dose was well tolerated (not escalated in non–anthracycline-based regimens); docetaxel dosing following AC or EC administration: 100 mg/m² for 3 cycles or 75 mg/m2 for first cycle and 100 mg/m² for subsequent 3 cycles, or 75 mg/m² for 4 cycles.
††Carboplatin dosing: AUC 6.
‡‡FEC dosing: 5-fluorouracil (500-600 mg/m²), epirubicin (90-120 mg/m²), and cyclophosphamide (500-600 mg/m²).
§§FAC dosing: 5-fluorouracil (500-600 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500-600 mg/m²).
‖‖Paclitaxel dosing: 80 mg/m².
¶¶AC dosing: doxorubicin (60 mg/m²) and cyclophosphamide (500-600 mg/m²) every 3 weeks or 2 weeks with GCSF support.
*** EC dosing: epirubicin (90-120 mg/m²) and cyclophosphamide (500-600 mg/m²) every 3 weeks or 2 weeks with GCSF support.

mBC treatment regimen[39,51]

Eligible patients with HER2+ mBC should receive fixed-dose SC combination of trastuzumab and pertuzumab every 3 weeks until disease progression or unmanageable toxicity, whichever occurs first, alongside at least 6 cycles of docetaxel.

- In CLEOPATRA (NCT00567190), it was recommended that docetaxel be administered for a minimum of 6 cycles.
  - The docetaxel dose could be decreased by 25% due to toxicity or increased to 100 mg/m² in those patients who could tolerate this dose
  - Fewer than 6 cycles were allowed for unmanageable toxicity
  - Comparable docetaxel exposure between the 2 treatment arms in CLEOPATRA
    - Docetaxel was administered for a median of 8 cycles in both treatment arms
- Fixed-dose SC combination of trastuzumab and pertuzumab should be continued until disease progression or unmanageable toxicity.
- If docetaxel is discontinued, fixed-dose SC combination of trastuzumab and pertuzumab may be continued on its own.

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ABBREVIATED PRESCRIBING INFORMATION

Perjeta® (Pertuzumab)

Active ingredient: Pertuzumab, for intravenous infusion
Please refer to locally approved Product Information prior the use of Pertuzumab IV.

Excipients: Glacial acetic acid, L histidine, sucrose, polysorbate 20 (produced from genetically modified maize), water for injection. **Therapeutic indications: Metastatic Breast Cancer (MBC):** PERJETA is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. **Early Breast Cancer (EBC):** PERJETA is indicated for use in combination with trastuzumab and chemotherapy for:1) The neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. 2) The adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence **Posology and method of administration:** The initial dose of PERJETA is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks by a dose of 420 mg administered as an intravenous infusion over 30 to 60 minutes. When administered with PERJETA, the recommended initial dose of trastuzumab is 8 mg/kg administered as a 90-minute intravenous infusion, followed every 3 weeks by a dose of 6 mg/kg administered as an intravenous infusion over 30 to 90 minutes. **Administration:** PERJETA, trastuzumab, and taxane should be administered sequentially. PERJETA and trastuzumab can be given in any order. Taxane should be administered after PERJETA and trastuzumab. An observation period of 30 to 60 minutes is recommended after each PERJETA infusion and before commencement of any subsequent infusion of trastuzumab or taxane . In Metastatic Breast Cancer (MBC), 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. In Neoadjuvant Treatment of Breast Cancer, PERJETA should be administered every 3 weeks for 3 to 6 cycles as part of one of the following treatment regimens for early breast cancer: •Four preoperative cycles of PERJETA in combination with trastuzumab and docetaxel followed by 3 postoperative cycles of fluorouracil, epirubicin, and cyclophosphamide(FEC) as given in NeoSphere. •Three or four preoperative cycles of FEC alone followed by 3 or 4 preoperative cycles of PERJETA in combination with docetaxel and trastuzumab as given in TRYPHAENA and BERENICE, respectively. •Six preoperative cycles of PERJETA in combination with docetaxel, carboplatin, and trastuzumab (TCH) (escalation of docetaxel above 75 mg/m2 is not recommended) as given in TRYPHAENA. •Four preoperative cycles of dose-dense doxorubicin and cyclophosphamide (ddAC) alonefollowed by 4 preoperative cycles of PERJETA in combination with paclitaxel andtrastuzumab as given in BERENICE. Following surgery, patients should continue to receive PERJETA and trastuzumab to complete 1 year of treatment (up to 18 cycles). In Adjuvant Treatment of Breast Cancer: PERJETA should be administered in combination with trastuzumab 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 as given in APHINITY. PERJETA and trastuzumab should start on Day 1 of the first taxane-containing cycle. **Contraindications:** PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients. **Special warnings and precautions for use: Infusion-associated reactions:** Hypersensitivity, anaphylactic reaction, acute infusion reaction, or cytokine release syndrome occurring during an infusion or on the same day as the infusion. Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of PERJETA. If a significant infusion-related reaction occurs, slow or interrupt the infusion, and administer appropriate medical therapies. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions. **Hypersensitivity reactions/anaphylaxis:** Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with treatment of PERJETA. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. PERJETA is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients. **Left ventricular dysfunction:** Decreases in LVEF have been reported with drugs that block HER2 activity, including PERJETA. Assess LVEF prior to initiation of PERJETA and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, discontinuation of PERJETA and trastuzumab should be strongly considered. 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 . **Embryo-Fetal Toxicity:** PERJETA can cause fetal harm when administered to a pregnant woman. PERJETA is a HER2/neu receptor antagonist. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy. Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA. Advise pregnant women and females of reproductive potential that exposure to ERJETA in combination with trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm, including embryo-fetal death or birth defects. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab **Pregnancy and lactation: Pregnancy:** PERJETA can cause fetal harm when administered to a pregnant woman. use of another HER2/neu receptor antagonist (trastuzumab) during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Monitor women who received PERJETA in combination with trastuzumab 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. **Pregnancy testing & Contraception:** Verify the pregnancy status of females of reproductive potential prior to the initiation of PERJETA and advise to use effective contraception during treatment and for 7 months following the last dose of PERJETA in combination with trastuzumab **Lactation:** data suggest that human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Consider the developmental and health benefits of breast feeding along with the mother's clinical need for PERJETA treatment and any potential adverse effects on the breastfed child from PERJETA or from the underlying maternal condition. **Adverse Reactions:** The most common adverse reactions were diarrhea, nausea, alopecia, fatigue, rash, peripheral neuropathy, vomiting , thrombocytopenia, anemia, constipation, headache, myalgia and mucosal inflammation

Full prescribing information is available upon request. In case of any adverse event occurring with Pertuzumab, please forward details to e-mail: dubai.drug_safety@roche.com or call +971544409415
Mode of Prescription: POM

Presentation: Vial with 14 ml concentrate for solution for infusion.contains 420 mg pertuzumab.

Marketing Authorization Holder: F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Date of preparation: 24th May 2018.
Leaflet: PI based on the US text dated Dec 2017.

WARNING: LEFT VENTRICULAR DYSFUNCTION and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Left Ventricular Dysfunction: PERJETA can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Evaluate cardiac function prior to and during treatment. Discontinue PERJETA treatment for a confirmed clinically significant decrease in left ventricular function.**
- **Embryo-fetal Toxicity: Exposure to PERJETA can result inembryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception.**

ABBREVIATED PRESCRIBING INFORMATION

Herceptin IV® (Trastuzumab)

Active ingredient: Trastuzumab, for Intravenous Infusion.

Please refer to locally approved Product Information prior the use of Herceptin IV.

Before the start of Herceptin therapy, overexpression of HER2 in the tumour tissue of the patient must have been demonstrated either by immunohistochemistry at a 3+ level or by molecular biology (detection of HER2 gene amplification using fluorescence in situ hybridisation [FISH] or chromogenic in situ hybridisation [CISH]).

Therapeutic indications: **Metastatic breast cancer,** Herceptin is indicated for the treatment of HER2-overexpressing metastatic breast cancer: a) as single-agent therapy in patients who have previously received one or more chemotherapy regimens for their metastatic disease, b) in combination with paclitaxel or docetaxel in patients who have not yet received chemotherapy for their metastatic disease, c) in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor-positive metastatic breast cancer and who have not yet received chemotherapy for their metastatic disease. No data are available on patients given Herceptin as adjuvant therapy in early breast cancer. **Early breast cancer** Herceptin is indicated for the treatment of patients with HER2-positive early breast cancer: **a)** following surgery, (neoadjuvant or adjuvant) chemotherapy and (if applicable) radiotherapy, **b)** following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. **c)** in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. **d)** in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin for locally advanced (including inflammatory) breast cancer or tumours >2 cm in diameter. **Metastatic gastric cancer or cancer of the gastroesophageal junction:** Herceptin in combination with capecitabine or intravenous 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received chemotherapy for their metastatic disease. Herceptin should only be used in patients with metastatic gastric cancer whose tumours overexpress HER2 defined by IHC2+ and confirmed by a positive FISH+ or silver in situ hybridisation (SISH) result, or by IHC 3+ determined in a validated test. **Posology and method of administration:** **Metastatic breast cancer – weekly schedule,** Herceptin should be administered by intravenous infusion. Do not administer as an intravenous bolus injection. The following loading and maintenance doses are recommended both for monotherapy and for combination with chemotherapy: **A)** *Monotherapy Initial dose:* The recommended initial dose is 4 mg Herceptin/kg body weight administered as a 90-minute intravenous infusion. Subsequent doses: The recommended weekly maintenance dose is 2 mg Herceptin/kg body weight. If the loading dose was well tolerated, this can be administered as a 30-minute infusion. **B)** *Combination therapy with paclitaxel or docetaxel:* The dosage of Herceptin in combination therapy is the same as that in monotherapy. Paclitaxel or docetaxel is administered on the day following the first dose of Herceptin treatment. Thereafter, they can be administered at 3-weekly intervals immediately after the subsequent Herceptin doses, provided that preceding Herceptin administration was well tolerated. For the dosage of paclitaxel or docetaxel, see the relevant prescribing information. **C)** *Administration in combination with an aromatase inhibitor:* The dosage of Herceptin in therapy based on this combination is the same as that in monotherapy. In patients receiving tamoxifen, treatment with tamoxifen must be discontinued at least one day before starting combination therapy. **Metastatic breast cancer – 3-weekly schedule:** As an alternative to weekly administration, the following 3‑weekly schedule is recommended in monotherapy as well as in combination with paclitaxel, docetaxel or an aromatase inhibitor: The loading dose of Herceptin is 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later. The subsequent Herceptin doses of 6 mg/kg body weight are repeated at 3-weekly intervals. Treatment is administered by infusion over approximately 90 minutes. If the initial dose was well tolerated, the maintenance dose can be administered as a 30-minute infusion. **Early breast cancer,** for the following treatment regimens, Herceptin is given until recurrence or for a total of 52 weeks. ***Weekly dosing:*** With weekly administration the initial dose is 4 mg/kg body weight, followed by 2 mg/kg body weight every week. ***Three-weekly dosing:*** With 3-weekly administration the recommended initial dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at 3-weekly intervals is 6 mg/kg body weight, beginning 3 weeks after the initial dose. When Herceptin is continued alone following combination with chemotherapy, 6 mg/kg is given at 3-weekly intervals. **Advanced gastric cancer or cancer of the gastroesophageal junction** – 3-weekly schedule: The initial dose is 8 mg/kg body weight, followed 3 weeks later by 6 mg/kg body weight. The subsequent 6 mg/kg Herceptin doses are repeated at 3-weekly intervals. Treatment is administered by infusion over approximately 90 minutes. If the initial dose was well tolerated, the maintenance dose can be administered as a 30-minute infusion. **Contraindications:** Herceptin is contraindicated in patients with known hypersensitivity to trastuzumab, hamster (CHO) cell protein or any other product or solvent excipient. Herceptin and anthracycline should not be given concurrently in the metastatic breast cancer or adjuvant treatment setting. In the neoadjuvant treatment setting concurrent administration of Herceptin and anthracyclines should be used with caution and only in chemotherapy-naïve patients. Herceptin is also contraindicated in patients who suffer from dyspnea at rest due to advanced malignancy or comorbidities. **Special warnings and precautions for use:** ***Infusion-related Reactions:*** Serious infusion-related reactions including dyspnea, hypotension, gasping or wheezing, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation and respiratory distress have been observed in rare patients during treatment with Herceptin. These adverse effects can occur as part of an infusion-related reaction or as a delayed reaction. ***Cardiotoxicity*** Patients treated with Herceptin may develop NYHA II-IV congestive heart failure or asymptomatic cardiac dysfunction. This has been observed during treatment with Herceptin alone or in combination with taxanes following anthracycline (doxorubicin or epirubicin) therapy. Heart failure may be moderate to severe and lead to death. Caution should be exercised in treating patients with increased cardiac risk (e.g. hypertension, documented coronary artery disease, congestive heart failure, diastolic dysfunction, older age). Herceptin and anthracyclines should not be given concurrently in the metastatic breast cancer or adjuvant treatment setting. In the neoadjuvant treatment setting concurrent administration of Herceptin and anthracyclines should be used with caution and only in chemotherapy-naïve patients **Undesirable effects:** The most serious and/or frequently reported undesirable effects during treatment with Herceptin are cardiotoxicity, infusion reactions, hematotoxicity (especially neutropenia) and pulmonary adverse events. NYHA II–IV cardiotoxicity (heart failure) is a common undesirable effect during treatment with Herceptin and maybe fatal in some cases. An estimated 40% of patients treated with Herceptin will experience infusion-related reactions of any kind. However, most of these infusion-related undesirable effects are of mild to moderate severity (based on NCI-CTC criteria) and occur mainly in the first treatments, particularly during the first three infusions and with decreasing frequency in subsequent infusions. Reactions include chills, fever, rash, nausea and vomiting, dyspnea and headache. Serious anaphylactic reactions necessitating immediate additional intervention occur very rarely and normally during the first or second infusion of Herceptin. Febrile neutropenia is very common. Common adverse events include anemia, leukopenia, thrombocytopenia and neutropenia. The frequency of hypoprothrombinemia is unknown. Serious pulmonary undesirable effects occur rarely during treatment with Herceptin, but have occasionally been associated with fatal outcome. They include pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema and respiratory failure

Mode of Prescription: POM
Presentation: 1 vial containing Herceptin (trastuzumab) 440 mg multiple-dose vials: Pack containing 1 vial of a white lyophilized powder for preparation of a concentrated solution for infusion with 440 mg trastuzumab and 1 vial of solvent contains:
water for injections containing 1.1% benzyl alcohol preservative (bacteriostatic water for injections).

Marketing Authorization Holder: F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Date of preparation: 25th September 2017

Full prescribing information is available upon request. In case of any adverse event occurring with Herceptin, please forward details to e-mail: dubai.drug_safety@roche.com or call +971544409415
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ABBREVIATED PRESCRIBING INFORMATION

PHESGO® (Pertuzumab and trastuzumab)
Active ingredients: Pertuzumab, Trastuzumab & hyaluronidase.

Solution for subcutaneous injection
Please refer to locally approved Product Information prior to the use of Phesgo.

Indications:
Early Breast Cancer (EBC): Phesgo is indicated in combination with chemotherapy for the:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence

Metastatic Breast Cancer (MBC): Phesgo is indicated in combination with docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Dosage and Administration:
Patient Selection: Patients treated with Phesgo should have HER2-positive tumor status assessed by a validated test. Administration: Phesgo therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients. Substitution by any other biological medicinal product requires the consent of the prescribing physician. Patients currently receiving intravenous pertuzumab and trastuzumab can switch to Phesgo

Phesgo is for subcutaneous (SC) use in the thigh only. Do not administer intravenously.

Recommended dosing and administration

	Dose (irrespective of body weight)	Approximate duration of SC injection	Observation time[ab]
Loading dose	1200 mg pertuzumab/600 mg trastuzumab)	8 minutes	30 minutes
Maintenance dose (every 3 weeks)	600 mg pertuzumab/ 600 mg trastuzumab	5 minutes	15 minutes

[a]Patients should be observed for injection-related and hypersensitivity reactions [b]Observation period should start following administration of Phesgo and be completed prior to any subsequent administration of chemotherapy.

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.

Assess left ventricular ejection fraction (LVEF) prior to initiation of Phesgo and at regular intervals during treatment. Refer to the full prescribing information for dose modification in the event of LVEF dysfunction.

Discontinue the injection immediately if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis).

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.

Contraindications:
Phesgo is contraindicated in patients with a known hypersensitivity to pertuzumab, trastuzumab, or hyaluronidase or any of the excipients.

Warning and Precautions:
Cardiomyopathy: Phesgo can cause hypertension, arrhythmias, left ventricular cardiac dysfunction, disabling cardiac failure, cardiomyopathy, and cardiac death. 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. 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. 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. 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. Pulmonary Toxicity: Phesgo can cause serious and fatal pulmonary toxicity. 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 chemotherapyinduced neutropenia. 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. 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. 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. Drug Interactions: Patients who receive anthracycline after stopping Phesgo may be at increased risk of cardiac dysfunction because of Phesgo's long washout period. 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.

Use in Special Populations:
Females and Males of Reproductive Potential. Phesgo can cause embryo-fetal harm when administered during pregnancy. Verify the pregnancy status of females of reproductive potential prior to the initiation of Phesgo. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of 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, report exposure details by e-mail: dubai.drug_safety@roche.com or mobile: 00971544409415. Lactation: 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. Consider the developmental and health benefits of breastfeeding 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. Pediatric Use: The safety and effectiveness of Phesgo in pediatric patients have not been established. Geriatric Use: 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. 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.

Adverse Reactions:
The most common adverse reactions with Phesgo were alopecia, nausea, diarrhea, anemia, and asthenia. The most common adverse reactions with pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy

Mode of Prescription: POM

Presentation:
·1200mg pertuzumab/600 mg trastuzumab/30000U hyaluronidase 15 mL solution in a vial
· 600 mg pertuzumab/600 mg trastuzumab/20000U hyaluronidase 10 mL solution in a vial

Excipients: L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, sucrose, polysorbate 20, L-methionine, water for injection Marketing Authorization Holder: F. Hoffmann-La Roche Ltd, Basel, Switzerland.

PI version date: Jun 2020

Date of preparation: 10 Feb 2021

Full prescribing information is available upon request. In case of any adverse event occurring with Phesgo please forward details to e-mail: dubai.drug_safety@roche.com Mobile: 00971544409415

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If a patient becomes pregnant while receiving PHESGO, or within 7 months following the last dose of PHESGO, please immediately report pregnancy to the local Roche Adverse Event Line dubai.drug_safety@roche.com Mobile: 00971544409415. Additional information will be requested during a PHESGO-exposed pregnancy and the first year of the infant's life. This will enable Roche to better understand the safety of PHESGO and to provide appropriate information to health authorities, healthcare providers, and patients. For additional information, please refer to the PHESGO local PI