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LEAF PHESGO VIAL ID
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PHESGO®
Pertuzumab and trastuzumab

Information as set forth in this label only applies to Phesgo

1. DESCRIPTION

1.1 THERAPEUTIC/PHARMACOLOGIC CLASS OF DRUG
Antineoplastic agents, recombinant humanized IgG1 monoclonal antibodies.

ATC code: L01XY02.

1.2 TYPE OF DOSAGE FORM
Solution for subcutaneous injection.

1.3 ROUTE OF ADMINISTRATION
Subcutaneous injection.

1.4 STERILE/RADIOACTIVE STATEMENT
Sterile product.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient(s): pertuzumab, trastuzumab.

Phesgo is a clear to opalescent solution, colourless to slightly brownish solution supplied in sterile, preservative-free, nonpyrogenic single-dose vials.

Single-dose vials contain:
- 1200 mg pertuzumab/600 mg trastuzumab/15 mL solution in a vial
- 600 mg pertuzumab/600 mg trastuzumab/10 mL solution in a vial

Excipients: Phesgo contains vorhyaluronidase alfa (recombinant human hyaluronidase rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated drugs when administered subcutaneously. All other excipients are L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dehydrate, polysorbate 20, L-methionine, water for injection.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)
Metastatic Breast Cancer
Phesgo is indicated in combination with docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer whose disease has relapsed after adjuvant therapy.

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 at high risk of recurrence (node positive or > 2 cm in diameter).

Phesgo is indicated in combination with chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence given by the presence of positive lymph nodes (see section *3.1.2 Clinical/Efficacy Studies*).

2.2 DOSAGE AND ADMINISTRATION
Patient Selection
Patients treated with Phesgo should have HER2-positive tumor status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥ 2.0 by in situ hybridization (ISH), assessed by a validated test.

To ensure accurate and reproducible results, the testing must be performed in a specialized laboratory, which can ensure validation of the testing procedures.

For full instructions on assay performance and interpretation, please refer to the package inserts of validated HER2 testing assays.

Administration of Phesgo
Phesgo therapy should only be administered under the supervision of a health care 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.

Switching treatment from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa) was investigated in study MO40628 (see section *2.6.1 Undesirable Effects* and section *3.1.2 Clinical/Efficacy Studies*).

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Phesgo.

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

Metastatic and Early Breast Cancer
For Phesgo dose recommendations in early and metastatic breast cancer refer to Table 1.

Table 1 Phesgo recommended dosing and administration

	Dose (irrespective of body weight)	Approximate duration of SC injection	Observation time[a, b]
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

In patients receiving intravenous pertuzumab and trastuzumab with < 6 weeks since their last dose, Phesgo should be administered 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, Phesgo should be administered as a loading dose of 1200 mg pertuzumab/600 mg trastuzumab, followed by a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks for subsequent administrations.

The 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 SC administration should preferably be injected at different sites.

In patients receiving a taxane, Phesgo should be administered prior to the taxane. When administered with Phesgo, the recommended initial dose of docetaxel is 75 mg/m^2.

In patients receiving an anthracycline-based regimen, Phesgo should be administered following completion of the entire anthracycline regimen.

Early Breast Cancer (EBC)
In the neoadjuvant setting (before surgery), it is recommended that patients are treated with Phesgo for three to six cycles depending on the regimen chosen in combination with chemotherapy (see section *3.1.2 Clinical/Efficacy Studies*).

In the adjuvant setting (after surgery), Phesgo should be administered for a total of one year (maximum 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. Phesgo treatment should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see section *3.1.2 Clinical/Efficacy Studies*).

Patients who start Phesgo in the neoadjuvant setting and have positive nodes before the start of their treatment should continue to receive adjuvant Phesgo to complete one year of treatment (maximum 18 cycles).

Metastatic Breast Cancer (MBC)
Phesgo should be administered in combination with docetaxel until disease progression or unmanageable toxicity. Treatment with Phesgo may continue even if treatment with docetaxel is discontinued.

Delayed or Missed Doses
If the time between two sequential doses is less than 6 weeks, the 600 mg pertuzumab/600 mg trastuzumab maintenance dose of Phesgo should be administered as soon as possible. Do not wait until the next planned dose.

If the time between two sequential injections is 6 weeks or more, the loading dose of 1200 mg pertuzumab/600 mg trastuzumab should be readminstered followed by the maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks thereafter.

Dose Modifications
No dose reductions of Phesgo are recommended.

For chemotherapy dose modifications, see relevant prescribing information.

Injection-related reactions
The injection should be slowed or paused if the patient experiences injection-related symptoms (see section *2.4 Warnings and Precautions)*.

Hypersensitivity/anaphylaxis
The injection should be discontinued immediately and permanently if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) (see section *2.4 Warnings and Precautions)*.

Left ventricular dysfunction
See section *2.4 Warnings and Precautions* for information on dose recommendations in the event of left ventricular dysfunction.

2.2.1 Special Dosage Instructions
Pediatric use
The safety and efficacy of Phesgo in children and adolescents (< 18 years) has not been established.

Geriatric use
No dose adjustment of Phesgo is required in patients ≥ 65 years of age (see sections *2.5.5 Geriatric Use* and *3.2.5 Pharmacokinetics in Special Populations*).

Renal impairment
Dose adjustments of Phesgo are not needed in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available (see section *3.2.5 Pharmacokinetics in Special Populations*).

Hepatic impairment
The safety and efficacy of Phesgo have not been studied in patients with hepatic impairment. No dose recommendation can be made for Phesgo (see section *3.2.5 Pharmacokinetics in Special Populations*).

2.3 CONTRAINDICATIONS
Phesgo is contraindicated in patients with a known hypersensitivity to pertuzumab, trastuzumab or any of the excipients.

2.4 WARNINGS AND PRECAUTIONS
2.4.1 General
In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Left ventricular dysfunction
Decreases in LVEF have been reported with drugs that block HER2 activity, including pertuzumab and trastuzumab. The incidence of symptomatic left ventricular systolic dysfunction (LVD [congestive heart failure]) was higher in patients treated with Perjeta in combination with Herceptin and chemotherapy compared to Herceptin and chemotherapy. In the adjuvant setting, the majority of cases of symptomatic heart failure reported were in patients who received anthracycline-based chemotherapy (see *2.6 Undesirable Effects*). Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF decreases based on studies with intravenous Perjeta in combination with Herceptin and chemotherapy.

Phesgo and/or intravenous Perjeta and Herceptin have not been studied in patients with: a pre-treatment LVEF value of < 55% (EBC) or < 50% (MBC); a prior history of congestive heart failure (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/m^2 of doxorubicin or its equivalent. Intravenous Perjeta in combination with Herceptin and chemotherapy has not been studied in patients with decreases in LVEF < 50% during prior Herceptin adjuvant therapy.

Assess LVEF prior to initiation of Phesgo and at regular intervals during treatment to ensure that LVEF is within normal limits (see *Table 2* below). If the LVEF declines as indicated in Table 2 and has not improved, or has declined further at the subsequent assessment, discontinuation of Phesgo should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Table 2 Dose recommendations for left ventricular dysfunction

	Pre-treatment LVEF:	Monitor LVEF every:	Withhold Phesgo for at least 3 weeks for an LVEF decrease to:		Resume Phesgo after 3 weeks if LVEF has recovered to:	
Metastatic Breast Cancer[a]	≥ 50%	~12 weeks	Either		Either	
			< 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
Early Breast Cancer	≥ 55%[b]	~12 weeks (once during neoadjuvant therapy)	< 50% with a fall of ≥ 10%-points below pre-treatment value		Either	
					≥ 50%	< 10%- points below pre-treatment value

[a] Based on intravenous Perjeta data (CLEOPATRA study)
[b] For patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting Phesgo

Injection/infusion-related reactions (IRRs)
Phesgo hasm been associated with injection-related reactions. Injection-related reactions were defined as any systemic reaction with symptoms such as fever, chills, headache, likely due to a release of cytokines occurring within 24 hours of administration of Phesgo. Close observation of the patient during and for 30 minutes after administration of the loading dose and during and for 15 minutes following the administration of the maintenance dose of Phesgo is recommended. If a significant injection-related reaction occurs, the injection should be slowed down or paused and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe injection-related reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see section *2.2 Dosage and Administration*). Although fatal outcomes resulting from injection-related reactions have not been observed with Phesgo, caution should be exercised as fatal infusion related-reactions have been associated with intravenous Perjeta in combination with intravenous Herceptin and chemotherapy.

Hypersensitivity reactions/anaphylaxis
Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with Phesgo, caution should be exercised as these have been associated with intravenous Perjeta in combination with Herceptin and chemotherapy (see section *2.6 Undesirable Effects*). Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Phesgo is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab, or to any of its excipients (see section *2.3 Contraindications*).

Embryo fetal toxicity
Exposure to pertuzumab and trastuzumab can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception.

Febrile neutropenia
Patients treated with pertuzumab, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, Herceptin and docetaxel, especially during the first 3 cycles of treatment (see section *2.6 Undesirable Effects*). In the CLEOPATRA trial in metastatic breast cancer, nadir neutrophil counts were similar in Perjeta-treated and placebo-treated patients. The higher incidence of febrile neutropenia in Perjeta-treated patients was associated with the higher incidence of mucositis and diarrhoea in these patients. Symptomatic treatment for mucositis and diarrhoea should be considered. No events of febrile neutropenia were reported after cessation of docetaxel.

Diarrhoea
Phesgo may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (> 65 years) may have a higher risk of diarrhoea compared with younger patients (< 65 years). Treat diarrhoea according to standard practice and guidelines. Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients, and in case of severe or prolonged diarrhoea. Interruption of treatment with Perjeta should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with Perjeta may be reinstated.

Pulmonary event
Severe pulmonary events have been reported with the use of trastuzumab in the postmarketing setting. These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other antineoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Phesgo. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

2.4.2 Drug Abuse and Dependence
There is no evidence that Phesgo has the potential for drug abuse and dependence.

2.4.3 Ability to Drive and Use Machines
Phesgo has a minor influence on the ability to drive and use machines. Injection-related reactions and dizziness may occur during treatment with Phesgo (see sections *2.4 Warnings and Precautions* and *2.6 Undesirable Effects*).

2.5 USE IN SPECIAL POPULATIONS
2.5.1 Females and Males of Reproductive Potential
Fertility
No specific fertility studies in animals have been performed to evaluate the effects of Phesgo.

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 pertuzumab for up to six month duration in cynomolgus monkeys (see section *3.3.3 Impairment of Fertility*).

Reproduction studies conducted in cynomologus monkeys with trastuzumab revealed no evidence of impaired fertility in female cynomologus monkeys (see section *3.3.3 Impairment of Fertility*).

Contraception
Women of childbearing potential including those who are partners of male patients should use effective contraception during treatment with Phesgo and for 7 months following the last dose of Phesgo.

2.5.2 Pregnancy
Phesgo should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

No clinical studies of Phesgo in pregnant women have been performed. Perjeta administered intravenously to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo fetal death (see section *3.3.4 Reproductive Toxicity*). In the postmarketing setting for Herceptin, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women.

Based on the aforementioned animal studies and postmarketing data, Phesgo has the potential to cause fetal harm when administered to a pregnant woman. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Phesgo, or if a patient becomes pregnant while receiving Phesgo or within 7 months following the last dose of Phesgo, close monitoring by a multidisciplinary team is desirable.

Labor and Delivery
The safe use of Phesgo during labor and delivery has not been established.

2.5.3 Lactation
As human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during Phesgo therapy and for 7 months after the last dose of Phesgo.

2.5.4 Pediatric Use
The safety and efficacy of Phesgo in pediatric patients below 18 years of age have not been established.

2.5.5 Geriatric Use
No overall differences in efficacy and safety of Phesgo was observed in patients ≥ 65 (n=26) and < 65 years of age (n=222).

However, with intravenous Perjeta in combination with Herceptin, the incidence of the following all Grade adverse events were at least 5% higher in patients ≥ 65 years of age (n=418) compared to patients < 65 years of age (n=2926): decreased appetite, anemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhoea.

2.5.6 Renal Impairment
See sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*.

2.5.7 Hepatic Impairment
The safety and efficacy of Phesgo in patients with hepatic impairment has not been studied.

2.6 UNDESIRABLE EFFECTS
2.6.1 Clinical Trials
Summary of the safety profile
The safety profile of Phesgo is based on data from the Phase III FEDERICA study in which HER2-positive early breast cancer patients were treated with either Phesgo (n=248) or intravenous Perjeta and Herceptin (n=252), in combination with chemotherapy.

The most common (≥ 5%) adverse drug reactions (ADRs) reported in patients treated with Phesgo or intravenous Perjeta in combination with Herceptin were diarrhoea, injection site reaction, infusion-related reactions, asthenia, fatigue, rash, ejection fraction decreased, and anemia.

The most common (≥ 1%) serious adverse events (SAEs) reported in patients treated with Phesgo or intravenous Perjeta in combination with Herceptin were febrile neutropenia, pyrexia, neutropenia, neutropenic sepsis, infusion-related reaction and neutrophil count decreased. SAEs were equally distributed between the Phesgo treatment arm and the intravenous Perjeta in combination with Herceptin treatment arm. The following adverse drug reactions were reported with a higher frequency (≥ 5%) with Phesgo compared to intravenous Perjeta in combination with Herceptin: alopecia 77% vs 70.2%, dyspnea 10.1% vs 4.4%, and fatigue 27.8% vs 22.6%.

Tabulated list of adverse drug reactions
The safety profile of Phesgo was overall consistent to the known safety profile of intravenous Perjeta in combination with Herceptin and chemotherapy as seen in the pertuzumab and trastuzumab-treated arms of the following studies (n=3344):
- CLEOPATRA, in which Perjeta was given in combination with Herceptin and docetaxel to patients with MBC (n=453)
- NEOSPHERE (n=309) and TRYPHAENA (n=218), in which neoadjuvant Perjeta was given in combination with Herceptin and chemotherapy to patients with locally advanced, inflammatory or EBC
- APHINITY, in which adjuvant Perjeta was given in combination with Herceptin and anthracycline-based or non-anthracycline-based, taxane-containing chemotherapy to patients with EBC (n=2364)

Table 3 presents ADRs that have been reported in association with the use of pertuzumab, trastuzumab and chemotherapy in the clinical trials and in the postmarketing setting.

As Perjeta and Herceptin is used in combination with chemotherapy, it is difficult to ascertain the causal relationship of an adverse reaction to a particular drug.

In this section, the following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000), and unknown (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Summary of adverse drug reactions reported from the pertuzumab, trastuzumab trials and in the postmarketing setting[a]

ADR (MedDRA preferred term) system organ class	Pertuzumab + trastuzumab + chemotherapy[b] Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
Blood and lymphatic system disorders			
Neutropenia	31.4	24.2	Very common
Anemia	24.8	5.7	Very common
Febrile neutropenia[d]	11.9	11.8	Very common
Leukopenia	10.8	6.1	Very common
Cardiac disorders			
Left ventricular dysfunction[e]	1.4	0.3	Common
Cardiac failure congestive[e]	0.1	< 0.1	Uncommon
Eye disorders			
Lacrimation increased	12.1	-	Very common
Gastrointestinal disorders			
Diarrhoea	67.9	8.9	Very common
Nausea	60.8	1.9	Very common
Vomiting	30.0	1.7	Very common
Stomatitis	24.9	1.6	Very common
Constipation	24.5	0.4	Very common
Dyspepsia	13.2	< 0.1	Very common
Abdominal pain	11.7	0.4	Very common
General disorders and administration site conditions			
Fatigue	44.3	3.3	Very common
Mucosal inflammation	23.2	1.5	Very common
Asthenia	20.9	1.5	Very common
Pyrexia	18.9	0.6	Very common
Edema peripheral	16.2	< 0.1	Very common
Injection site reactions[f]	12.9	0	Very common
Immune system disorders			
Hypersensitivity	3.3	0.4	Common
Drug hypersensitivity	2.5	0.4	Common
Infections and infestations			
Nasopharyngitis	12.8	< 0.1	Very common
Upper respiratory tract infection	9.5	0.3	Common
Paronychia	3.9	< 0.1	Common
Metabolism and nutrition disorders			
Decreased appetite	23.1	0.8	Very common
Tumor lysis syndrome[g]	Unknown		
Musculoskeletal and connective tissue disorders			
Arthralgia	24.6	0.7	Very common
Myalgia	24.3	0.8	Very common
Pain in extremity	10.0	0.2	Very common
Nervous system disorders			
Dysgeusia	22.7	< 0.1	Very common
Headache	21.8	0.4	Very common
Peripheral sensory neuropathy	15.7	0.5	Very common
Neuropathy peripheral	14.7	0.7	Very common
Dizziness	11.2	0.1	Very common
Paraesthesia	10.2	0.4	Very common
Psychiatric disorders			
Insomnia	15.9	0.2	Very common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	15.6	< 0.1	Very common
Cough	15.5	< 0.1	Very common
Dyspnea	11.5	0.5	Very common
Pleural effusion	0.9	< 0.1	Uncommon
Skin and subcutaneous tissue disorders			
Alopecia	63.1	< 0.1	Very common
Rash	26.4	0.5	Very common
Nail disorder	12.9	0.3	Very common
Pruritus	12.9	< 0.1	Very common
Dry skin	11.7	< 0.1	Very common
Vascular disorders			
Hot flush	15.7	0.1	Very common

[a] Table 3 shows pooled data from the overall treatment period in CLEOPATRA; from the neoadjuvant treatment period in NEOSPHERE and TRYPHAENA; and from the treatment period of APHINITY). Additionally, Table 3 shows an ADR specific to the Phesgo route of administration that has been reported in FEDERICA.
[b] In NEOSPHERE, 108 patients received Perjeta + Herceptin alone without docetaxel and 94 patients received Perjeta + docetaxel without Herceptin.
[c] In CLEOPATRA, 45 patients who were randomized to receive placebo and who had no prior exposure to Perjeta, had crossed over to receive Perjeta and are included in the 3344 patients treated with Perjeta.
[d] In this table this denotes an adverse reaction that has been reported in association with a fatal outcome.
[e] The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA preferred terms reported in the individual studies.
[f] Observed with Phesgo only.
[g] Identified in the postmarketing setting.

Description of selected adverse drug reactions from clinical trials

Phesgo

Left ventricular dysfunction
In FEDERICA, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to < 50% was 0.4% of Phesgo-treated patients vs 0% of intravenous Perjeta and Herceptin-treated patients.
Of the patients who experienced symptomatic heart failure, all Phesgo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to < 50% (confirmed by secondary LVEF) were reported in 0.4% of Phesgo-treated patients and 0.8% of intravenous Perjeta and Herceptin-treated patients, of whom none of the Phesgo-treated patients or intravenous Perjeta and Herceptin-treated patients had recovered at the data cutoff.

Injection/infusion-related reactions
In FEDERICA, an injection/infusion-related reactions was defined as any systemic reaction reported within 24 hours of Phesgo or intravenous Perjeta in combination with Herceptin administration. Injection-related reactions were reported in 1.2% of Phesgo-treated patients and infusion-related reactions were reported in 10.3% of intravenous Perjeta and Herceptin-treated patients.

Injection site reactions (defined as any local reaction reported within 24 hours of Phesgo) were reported in 12.9% of Phesgo treated patients and were all Grade 1 or 2 events.

Hypersensitivity reactions/anaphylaxis
In FEDERICA, the overall frequency of hypersensitivity/anaphylaxis reported events related to HER2-targeted therapy was 1.6% in both the Phesgo-treated patients and intravenous Perjeta and Herceptin-treated patients, of which none were NCI-CTCAE (version 4) Grade 3-4 (see section *2.4 Warnings and Precautions*).

Laboratory abnormalities
In FEDERICA, the incidence of NCI-CTCAE Grade 3-4 decreases in neutrophil counts were balanced in the Phesgo and intravenous Perjeta and Herceptin groups.

Intravenous Perjeta and Herceptin

Left ventricular dysfunction
In CLEOPATRA, the incidence of LVD during study treatment was higher in the placebo-treated group than the Perjeta-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the Perjeta-treated group (1.8% in the placebo-treated group vs 1.5% in the Perjeta-treated group) (see section *2.4 Warnings and Precautions*).

In NEOSPHERE, in which patients received four cycles of Perjeta as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the Perjeta, Herceptin and docetaxel-treated group (7.5%) compared to the Herceptin and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the Perjeta and Herceptin-treated group.

In TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with Perjeta plus Herceptin and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by Perjeta plus Herceptin and docetaxel; 9.3% in the group treated with Perjeta plus Herceptin and docetaxel following FEC; and 6.6% in the group treated with Perjeta in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with Perjeta plus Herceptin and docetaxel following FEC *(this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus Herceptin and docetaxel)* and also 1.3% in the group treated with Perjeta in combination with TCH. No patients in the group treated with Perjeta plus Herceptin and FEC followed by Perjeta plus Herceptin and docetaxel experienced symptomatic LVD.

In the neoadjuvant period of the BERENICE trial, the incidence of NYHA Class III/IV symptomatic LVD (congestive heart failure according to NCI-CTCAE v.4) was 1.5% in the group treated with dose dense AC followed by Perjeta plus Herceptin and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by Perjeta in combination with Herceptin and docetaxel. The incidence of asymptomatic LVD (PT ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by Perjeta plus Herceptin and paclitaxel and 3.5% in the group treated with FEC followed by Perjeta plus Herceptin and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to < 50% was < 1% (0.6% of pertuzumab-treated patients vs 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7% of pertuzumab-treated patients and 66.7% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to < 50% were reported in 2.7% of pertuzumab-treated patients and 2.8% of placebo-treated patients, of whom 79.7% of pertuzumab-treated patients and 80.6% of placebo-treated patients had recovered at the data cutoff.

Infusion-related reactions
An infusion-related reactions was defined in the pivotal trials as any event reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. In CLEOPATRA, the initial dose of Perjeta was given the day before Herceptin and docetaxel to allow for the examination of Perjeta associated reactions. On the first day when only Perjeta was administered, the overall frequency of infusion-related reactions was 9.8% in the placebo-treated group and 13.2% in the Perjeta-treated group, with the majority of reactions being mild or moderate. The most common infusion-related reactions (≥ 1.0%) in the Perjeta-treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion related reactions (≥ 1.0%) in the Perjeta-treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia, and vomiting (see section *2.4 Warnings and Precautions*).

In neoadjuvant and adjuvant trials, Perjeta was administered on the same day as the other study treatment drugs. Infusion-related reactions occurred in 18.6%-25.0% of patients on the first day of Perjeta administration (in combination with Herceptin and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being mild or moderate.

Hypersensitivity/anaphylaxis
In the CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reported events was 9.3% in the placebo-treated patients and 11.3% in the Perjeta-treated patients, of which 2.5% and 2.0% were NCI-CTCAE (version 3) Grade 3-4, respectively. Overall, 2 patients in placebo-treated group and 4 patients in the Perjeta-treated group experienced anaphylaxis (see section *2.4 Warnings and Precautions*).

Overall, the majority of hypersensitivity reactions was mild or moderate in severity and resolved upon treatment. Based on modifications made to study treatment, most reactions were assessed as secondary to docetaxel infusions.

In neoadjuvant and adjuvant trials, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the Perjeta and docetaxel-treated group experienced anaphylaxis. In both TRYPHAENA and APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the Perjeta and TCH treated group (13.2% and 7.6% respectively), of which 2.6% and 1.3% of events, respectively were NCI-CTCAE Grade 3-4.

Febrile neutropenia
In the CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (63.0% of patients in the Perjeta-treated group and 58.3% of patients in the 12 placebo-treated group), of which the majority were neutropenic events (see section *2.4 Warnings and Precautions*). Febrile neutropenia occurred in 13.7% of Perjeta-treated patients and 7.6% of placebo-treated patients. In both treatment groups, the proportion of patients experiencing febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed among Asian patients in both treatment groups compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the Perjeta-treated group (25.8%) compared with the placebo-treated group (11.3%).

In the NEOSPHERE trial, 8.4% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with Herceptin and docetaxel. In the TRYPHAENA trial, febrile neutropenia occurred in 17.1% of patients treated with neoadjuvant Perjeta + TCH, and 9.3% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel following FEC. In TRYPHAENA, the incidence of febrile neutropenia was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given. As in the CLEOPATRA trial, a higher incidence of neutropenia and febrile neutropenia was observed among Asian patients compared with other patients in both neoadjuvant trials. In NEOSPHERE, 8.3% of Asian patients treated with neoadjuvant Perjeta, Herceptin and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant Herceptin and docetaxel.

In the APHINITY trial, febrile neutropenia occurred in 12.1% of Perjeta-treated patients and 11.1% of placebo-treated patients. As in the CLEOPATRA, TRYPHAENA, and NEOSPHERE trials, a higher incidence of febrile neutropenia was observed among Perjeta-treated Asian patients compared with other races in the APHINITY trial (15.9% of Perjeta-treated patients and 9.9% of placebo-treated patients).

Diarrhoea
In the CLEOPATRA, in metastatic breast cancer, diarrhoea occurred in 68.4% of Perjeta-treated patients and 48.7% of placebo-treated patients (see section *2.4 Warnings and Precautions*). Most events were mild to moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhoea was 9.3% in Perjeta-treated patients vs 5.1% in placebo-treated patients. The median duration of the longest episode was 18 days in Perjeta-treated patients and 8 days in placebo-treated patients. Diarrhoeal events responded well to proactive management with anti-diarrhoeal agents.

In the NEOSPHERE trial, diarrhoea occurred in 45.8% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel compared with 33.6% of patients treated with Herceptin and docetaxel. In the TRYPHAENA trial, diarrhoea occurred in 72.3% of patients treated with neoadjuvant Perjeta+TCH and 61.4% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel following FEC. In both studies most events were mild to moderate in severity.

In the APHINITY trial, a higher incidence of diarrhoea was reported in the Perjeta-treated arm (71.2%) compared to the placebo arm (45.2%). Grade ≥ 3 diarrhoea was reported in 9.8% of patients in the Perjeta arm vs 3.7% in the placebo arm. The majority of the reported events were Grade 1 or 2 in severity. The highest incidence of diarrhoea (all Grades) was reported during the targeted therapy+taxane chemotherapy period (61.4% of patients in the Perjeta arm vs 33.8% of patients in the placebo arm). The incidence of diarrhoea was much lower after chemotherapy cessation, affecting 18.1% of patients in the Perjeta arm vs 9.2% of patients in the placebo arm in the postchemotherapy targeted therapy period.

Rash
In the CLEOPATRA, in metastatic breast cancer, rash occurred in 51.7% of Perjeta-treated patients, compared with 38.9% of placebo-treated patients. Most events were Grade 1 or 2 in severity, occurred in the first two cycles, and responded to standard therapies, such as topical or oral treatment for acne.

In the NEOSPHERE trial, rash occurred in 40.2% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel compared with 29.0% of patients treated with Herceptin and docetaxel. In the TRYPHAENA trial, rash occurred in 36.8% of patients treated with neoadjuvant Perjeta+TCH and 20.0% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel following FEC. The incidence of rash was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, independent of the chemotherapy given.

In the APHINITY trial, the adverse event of rash occurred in 25.8% of patients in Perjeta arm vs 20.3% of patients in placebo arm. The majority of rash events were Grade 1 or 2.

Laboratory Abnormalities
In the CLEOPATRA and NEOSPHERE, and APHINITY the incidence of NCI-CTCAE Grade 3-4 decreases in neutrophil counts were balanced in the Perjeta-treated and control groups.

Switching treatment from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa)
Switching from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa) was well tolerated by patients and did not reveal any new or clinically relevant safety concerns and the adverse events experienced were in line with those studied in FEDERICA and in previous studies using intravenous pertuzumab and trastuzumab administration (see section *3.1.2 Clinical/Efficacy Studies*).

2.6.2 Postmarketing Experience
Not applicable.

2.7 OVERDOSE
There is no experience with overdose of Phesgo in human clinical trials. The highest Phesgo dose tested is 1200 mg pertuzumab/600 mg trastuzumab.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No formal drug-drug interaction studies have been performed.

Intravenous Perjeta
A sub-study in 37 patients in the pivotal trial CLEOPATRA showed no evidence of drug-drug interaction between Perjeta and Herceptin and between Perjeta and docetaxel. In addition, no clinically relevant pharmacokinetic interaction of coadministered docetaxel or Herceptin on Perjeta was evident, based on the population pharmacokinetics analysis. This lack of drug-drug interaction was confirmed by pharmacokinetic data from the NEOSPHERE and APHINITY studies.

Five studies evaluated the effects of Perjeta on the pharmacokinetics of coadministered cytotoxic agents, docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin, and erlotinib. There was no evidence of any pharmacokinetics interaction between Perjeta and any of these agents. The pharmacokinetics of Perjeta in these studies was comparable to those observed in single-agent studies.

Intravenous Herceptin
There have been no formal drug interaction studies performed with Herceptin in humans. Clinically significant interactions between Herceptin and the concomitant medications used in clinical trials have not been observed.

In studies where Herceptin was administered in combination with docetaxel or carboplatin, the pharmacokinetics of these medications was not altered nor was the pharmacokinetics of Herceptin altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of Herceptin. However, Herceptin may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. No changes were observed in Herceptin concentrations in the presence of paclitaxel and doxorubicin.

The results of a drug interaction sub-study evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without Herceptin suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus Herceptin. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Herceptin. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Herceptin.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action
Pertuzumab and trastuzumab are recombinant humanized immunoglobulin (Ig)G1κ monoclonal antibodies, which target the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab and trastuzumab bind to distinct HER2 epitopes, subdomains II and IV, respectively, without competing and have complementary mechanisms for disrupting HER2 signaling. This results in augmented antiproliferative activity *in vitro* and *in vivo* when pertuzumab and trastuzumab are given in combination.

Additionally, the Fc portion of both their IgG1 framework provides for potent activation of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, both pertuzumab and trastuzumab ADCC are exerted preferentially on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

3.1.2 Clinical/Efficacy Studies
This section presents the clinical experience from Phesgo and intravenous Perjeta in combination with Herceptin patients with HER2-positive early and metastatic breast cancer.
HER2 overexpression in all trials outlined below was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio ≥ 2.0.

Early Breast Cancer

Fixed-dose combination of pertuzumab and trastuzumab Phesgo

FEDERICA WO40324
FEDERICA is an open-label, multicenter, randomized study conducted in 500 patients with HER2-positive early breast cancer that is operable or locally advanced (including inflammatory) breast cancer with a tumor size > 2 cm or node-positive in the neoadjuvant and adjuvant setting. Patients were randomized to receive 8 cycles of neoadjuvant chemotherapy with concurrent administration of 4 cycles of either Phesgo or intravenous Perjeta and Herceptin during Cycles 5-8. 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 Perjeta and Herceptin as treated prior to surgery, for an additional 14 cycles, to complete 18 cycles of HER2-targeted therapy. Patients also received adjuvant radiotherapy and endocrine therapy as per local practice. In the adjuvant setting, substitution of intravenous Herceptin for subcutaneous Herceptin SC was permitted at investigator discretion.
HER2-targeted therapy was administered every 3 weeks according to Table 4 as follows:

Table 4 Dosing and administration of Phesgo, intravenous Perjeta, intravenous Herceptin, and subcutaneous Herceptin

Medication	Administration	Dose	
		Loading	Maintenance
Phesgo	Subcutaneous injection	1200 mg/600 mg	600 mg/600 mg
Perjeta	Intravenous infusion	840 mg	420 mg
Herceptin	Intravenous infusion	8 mg/kg	6 mg/kg
Herceptin	Subcutaneous injection	600 mg	

FEDERICA was designed to demonstrate non-inferiority of the pertuzumab Cycle 7 (i.e. pre-dose Cycle 8) serum C_{trough} of pertuzumab within Phesgo compared with intravenous Perjeta (primary endpoint). Additional secondary endpoints included non-inferiority of the Cycle 7 serum trastuzumab C_{trough} of trastuzumab within Phesgo compared with intravenous trastuzumab, efficacy [total pathological complete response (tpCR)], and safety outcomes. Demographics were well balanced between the two treatment arms and the median age of patients treated in the study was 51 years. The majority of patients had hormone receptor-positive disease (61.2%), node-positive disease (57.6%), and were Caucasian (65.8%).

Non-inferiority of the pertuzumab and trastuzumab exposure from Phesgo was demonstrated (see section *3.2 Pharmacokinetic Properties*). The analysis of secondary efficacy endpoint, tpCR, defined as an absence of invasive disease in the breast and axilla (ypT0/is, ypN0), is shown in Table 5.

Table 5 Summary of total pathological Complete Response (tpCR)

	Phesgo (n=248)	Intravenous Perjeta + Herceptin (n=252)
tpCR (ypT0/is, ypN0)	148 (59.7%)	150 (59.5%)
Exact 95% CI for tpCR Rate[1]	(53.28, 65.84)	(52.18, 65.64)
Difference in tpCR rate (SC minus IV arm)	0.15	
95% CI for the difference in tpCR[2] rate	-8.67 to 8.97	

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

Intravenous Perjeta and Herceptin

Neoadjuvant Treatment

NEOSPHERE (WO20697)
NEOSPHERE is a multicenter, randomized Phase II clinical trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. Patients were randomized to receive one of four neoadjuvant regimens prior to surgery as follows: Herceptin plus docetaxel, Perjeta plus Herceptin and docetaxel, Perjeta plus Herceptin, or Perjeta plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen (ER) or progesterone (PgR) positivity.

Perjeta and Herceptin were administered intravenously as outlined in Table 4 for 4 cycles. Following surgery all patients received three cycles of 5-Fluorouracil (600 mg/m²), epirubicin (90 mg/m²), cyclophosphamide (600 mg/m²) (FEC) given intravenously every three weeks and Herceptin administered intravenously every three weeks to complete one year of therapy. Patients in the Perjeta plus Herceptin and docetaxel arm received docetaxel every three weeks for four cycles prior to FEC after surgery so that all patients received equivalent cumulative doses of the chemotherapeutic agents and Herceptin.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). Secondary efficacy endpoints were clinical response rate, breast conserving surgery rate (T2-3 only), disease-free survival (DFS), and PFS. Additional exploratory pCR rates included nodal status (ypT0/isN0 and ypT0N0).

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (71%)) and all were female. Overall 7% of patients had inflammatory breast cancer, 32% had locally advanced breast cancer and 61% had operable breast cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER positive and/or PgR positive).

The efficacy results are summarized in Table 6. A statistically significant and clinically meaningful improvement in pCR rate (ypT0/is) was observed in patients receiving Perjeta plus Herceptin and docetaxel compared to patients receiving Herceptin and docetaxel (45.8% vs 29.0%, p value= 0.0141). A consistent pattern of results was observed regardless of pCR definition.

Pathological complete response (pCR) rates as well as the magnitude of improvement with Perjeta were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (5.9% to 26.0% and 27.3% to 63.2%, respectively).

TRYPHAENA (BO22280)
TRYPHAENA is a multicenter, randomized Phase II clinical study conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer. Patients were randomized to receive one of three neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with Perjeta and Herceptin, 3 cycles of FEC alone followed by 3 cycles of docetaxel and Herceptin in combination with Perjeta, or 6 cycles of TCH in combination with Perjeta. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and/or PgR positivity.

Perjeta and Herceptin were administered intravenously as outlined in Table 4. 5-Fluorouracil (500 mg/m²), epirubicin (100 mg/m²), cyclophosphamide (600 mg/m²) were given intravenously every three weeks for 3 cycles. Docetaxel was given as an initial dose of 75 mg/m² IV infusion every three weeks with the option to escalate to 100 mg/m² at the investigator's discretion if the initial dose was well tolerated. However, in the Perjeta in combination with TCH arm, docetaxel was given intravenously at 75 mg/m² and no escalation was permitted and carboplatin (AUC 6) was given intravenously every three weeks. Following surgery all patients received Herceptin to complete one year of therapy, which was administered intravenously every 3 weeks.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see section *2.6 Undesirable Effects*). Secondary efficacy endpoints were pCR rate in the breast (ypT0/is), DFS, PFS and OS.

Demographics were well balanced (median age was 49-50 years old, the majority were Caucasian (71%)) and all were female. Overall 6% of patients had inflammatory breast cancer, 25% had locally advanced breast cancer and 69% had operable breast cancer, with approximately half the patients in each treatment group had ER-positive and/or PgR-positive disease.

High pCR rates were observed in all 3 treatment arms (see *Table 6*). A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (46.2% to 50.0% and 65.0% to 83.8%, respectively).

Table 6 NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Summary of efficacy (ITT population)

	NEOSPHERE (WO20697)				TRYPHAENA (BO22280)		
Parameter	**T+D n=107**	**Ptz+T+D n=107**	**Ptz+T n=107**	**Ptz+D n=96**	**Ptz+T+FEC/ Ptz+T+D n=73**	**FEC/ Ptz+T+D n=75**	**Ptz+TCH n=77**
ypT0/is n (%) [95% CI][1]	31 (29.0%) [20.6; 38.5]	49 (45.8%) [36.1; 55.7]	18 (16.8%) [10.3; 25.3]	23 (24.0%) [15.8; 33.7]	45 (61.6%) [49.5; 72.8]	43 (57.3%) [45.4; 68.7]	51 (66.2%) [54.6; 76.6]
Difference in pCR rates[2] [95% CI][3]		+16.8 % [3.5; 30.1]	-12.2 % [-23.8; -0.5]	-21.8 % [-35.1; -8.5]	NA	NA	NA
p-value (with Simes corr. for CMH test)[4]		0.0141 (vs T+D)	0.0198 (vs T+D)	0.0030 (vs Ptz+T+D)	NA	NA	NA
ypT0/is N0 n (%) [95% CI]	23 (21.5%) [14.1; 30.5]	42 (39.3%) [30.3; 49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7; 26.8]	41 (56.2%) [44.1; 67.8]	41 (54.7%) [42.7; 66.2]	49 (63.6%) [51.9; 74.3]
ypT0 N0 n (%) [95% CI]	13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0; 42.5]	6 (5.6%) [2.1; 11.8]	13 (13.2%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]	40 (51.9%) [40.3; 63.5]
Clinical Response[5]	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (91.8%)	71 (94.7%)	69 (89.6%)

Key to abbreviations (Table 6): T: Herceptin; D: docetaxel; Ptz: Perjeta; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab.
1. 95% CI for one sample binomial using Pearson-Clopper method.
2. Treatment Ptz+T+D and Ptz+T are compared with T+D, while Ptz+D is compared with Ptz+T+D.
3. Approximate 95% CI for difference of two rates using Hauck-Anderson method.
4. p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment.
5. Clinical response represents patients with a best overall response of CR or PR during the neoadjuvant period (in the primary breast lesion).

BERENICE (WO29217)
BERENICE is a non-randomized, open-label, multicenter, multinational, Phase II trial conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer.

The BERENICE study included two parallel groups of patients. Patients considered suitable for neoadjuvant treatment with Herceptin plus anthracycline/taxane-based chemotherapy were allocated to receive one of the two following regimens prior to surgery as follows:

Cohort A - 4 cycles of two-weekly doxorubicin and cyclophosphamide (dose dense AC) followed by 4 cycles of Perjeta in combination with Herceptin and paclitaxel.

Cohort B - 4 cycles of FEC followed by 4 cycles of Perjeta in combination with Herceptin and docetaxel.

Perjeta and Herceptin were administered intravenously as outlined in Table 4. Doxorubicin 60 mg/m² IV and cyclophosphamide 600 mg/m² IV were administered every 2 weeks (ddAC) for four cycles (Cycles 1-4) with G-CSF (granulocyte colony stimulating factor) support at investigator discretion, followed by paclitaxel 80 mg/m² IV weekly for 12 weeks (Cycles 5-8), with Perjeta and Herceptin every 3 weeks during Cycles 5-8 (from the start of paclitaxel; four cycles of Perjeta and Herceptin in total during the neoadjuvant period). 5-Fluorouracil (500 mg/m²), epirubicin (100 mg/m²), cyclophosphamide (600 mg/m²) were given intravenously every three weeks for 4 cycles. Docetaxel was given at an initial dose of 75 mg/m² IV infusion every three weeks with the option to escalate to 100 mg/m² at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received Perjeta and Herceptin which were administered intravenously every 3 weeks, to complete one year of therapy.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see section *2.6 Undesirable Effects*). Key secondary endpoints at the time of primary analysis were neoadjuvant safety and pCR rate in the breast and nodes (i.e. ypT0/is ypN0). Long-term clinical and safety outcomes will also be assessed (IDFS, EFS and OS, not yet available).

Demographics of the patients were well balanced between the groups. The median age of the patients was 49 years, the majority of patients were Caucasian (83%) and all but one patient was female. Approximately two-thirds of patients (64.3% [n=128] in Cohort A and 61.7% [n=124] in Cohort B) had hormone receptor-positive disease.

High pCR rates were observed in both treatment arms, with pCR (ypT0/is ypN0) rates of 61.8% in Cohort A and 60.7% in Cohort B. A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors in both Cohorts (51.6% to 81.5% and 57.3% to 68.0%, respectively).

Adjuvant Treatment

APHINITY (BO25126)
APHINITY is a multicenter, randomized, double-blind, placebo-controlled Phase III trial conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. Patients were then randomized to receive Perjeta or placebo, in combination with adjuvant Herceptin and chemotherapy. Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:
- 3 or 4 cycles of FEC or 5-fluorouracil, doxorubicin and cyclophosphamide (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
- 6 cycles of docetaxel in combination with carboplatin

Perjeta and Herceptin were administered intravenously as outlined in Table 4 starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (maximum 18 cycles) or until recurrence, withdrawal of consent or unmanageable toxicity. Standard doses of 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel and carboplatin were administered. After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per local clinical standard.

The primary endpoint of the study was invasive disease-free survival (IDFS), defined as the time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause.

Demographics were well balanced between the two treatment arms. The median age was 51 years, and over 99% of patients were female. The majority of patients had node-positive (63%) and/or hormone receptor-positive disease (64%), and were Caucasian (71%).

After a median follow-up to 45.4 months, the APHINITY study demonstrated 19% (hazard ratio [HR]=0.81) reduction in risk of

recurrence or death in patients randomized to receive Perjeta compared with patients randomized to receive placebo.

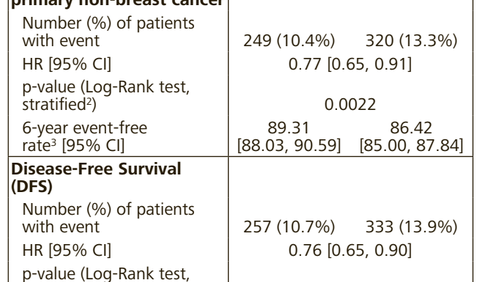
The efficacy results from the APHINITY trial are summarized in Table 7 and in Figures 1 and 2.

Table 7 Overall efficacy (ITT population)

	Perjeta + Herceptin + chemotherapy n=2400	Placebo + Herceptin + chemotherapy n=2404
Primary Endpoint		
Invasive Disease-Free Survival (IDFS)		
Number (%) of patients with event	221 (9.2%)	287 (11.9%)
HR [95% CI]	0.76 [0.64, 0.91]	
p-value (Log-Rank test, stratified[2])	0.0025	
6-year event-free rate[3] [95% CI]	90.56 [89.35, 91.77]	87.76 [86.40, 89.13]
Secondary Endpoints[1]		
IDFS including second primary non-breast cancer		
Number (%) of patients with event	249 (10.4%)	320 (13.3%)
HR [95% CI]	0.77 [0.65, 0.91]	
p-value (Log-Rank test, stratified[2])	0.0022	
6-year event-free rate[3] [95% CI]	89.31 [88.03, 90.59]	86.42 [85.00, 87.84]
Disease-Free Survival (DFS)		
Number (%) of patients with event	257 (10.7%)	333 (13.9%)
HR [95% CI]	0.76 [0.65, 0.90]	
p-value (Log-Rank test, stratified[2])	0.0012	
6-year event-free rate[3] [95% CI]	88.99 [87.69, 90.29]	86.03 [84.59, 87.47]
Overall Survival (OS)[4]		
Number (%) of patients with event	125 (5.2%)	147 (6.1%)
HR [95% CI]	0.85 [0.67, 1.07]	
p-value (Log-Rank test, stratified[2])	0.1700	
6-year event-free rate[3] [95% CI]	94.78 [93.85, 95.71]	93.93 [92.93, 94.92]
Recurrence-Free Interval (RFI)		
Number (%) of patients with event	169 (7.0%)	233 (9.7%)
HR [95% CI]	0.72 [0.59, 0.88]	
p-value (Log-Rank test, stratified[2])	0.0013	
6-year event-free rate[3] [95% CI]	92.49 [91.40, 93.59]	89.91 [88.66, 91.16]
Distant Recurrence-Free Interval (DRFI)		
Number (%) of patients with event	149 (6.2%)	194 (8.1%)
HR [95% CI]	0.76 [0.62, 0.95]	
p-value (Log-Rank test, stratified[2])	0.0134	
6-year event-free rate[3] [95% CI]	93.37 [92.34, 94.40]	91.57 [90.42, 92.72]

Key to abbreviations (Table 7): HR: Hazard Ratio; CI: Confidence Intervals
1. Hierarchical testing applied for all secondary endpoints with the exception of RFI and DRFI.
2. All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
3. 6-year event-free rate derived from Kaplan-Meier estimates.
4. Data from second interim analysis.

Figure 1 Kaplan-Meier curve of invasive disease-free survival



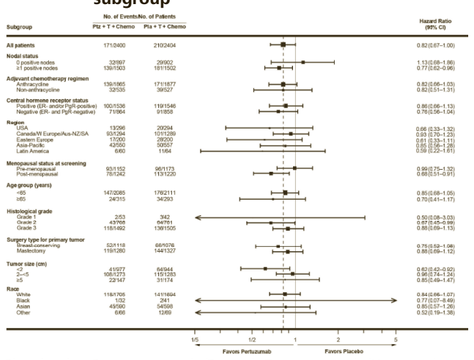
Pla=placebo; Ptz=pertuzumab (Perjeta); T=trastuzumab (Herceptin)

The estimate of IDFS at 4-years was 92.3% in the Perjeta-treated group vs 90.6% in the placebo-treated group. At the time of the estimate the median follow-up was 45.4 months.

Results of Subgroup Analysis

Consistent results were observed across the majority of prespecified patient subgroups. The benefits of Perjeta were more apparent for patients in certain high risk groups, notably patients with node-positive disease (see *Figure 2* below).

Figure 2 Forest plot of invasive disease-free survival by subgroup



Pla=placebo; Ptz=pertuzumab (Perjeta); T=trastuzumab (Herceptin)

Estimates of IDFS rates in the node-positive subgroup were 87.9% vs 83.4% at 6 years in Perjeta-treated patients vs the placebo-treated patients, respectively. In the node-negative subgroup estimates of IDFS rates were 95.0% vs 94.9% at 6 years in Perjeta-treated patients vs placebo-treated patients, respectively.

Patient Reported Outcomes (PRO)

Secondary endpoints included the assessment of patient-reported global health status, role and physical function, and treatment symptoms using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. In the analyses of patient-reported outcomes, a 10-point difference was considered clinically meaningful.

Patients' physical function, global health status and diarrhoea scores showed a clinically meaningful change during chemotherapy in both treatment arms. The mean decrease from baseline at that time for physical function was -10.7 (95% CI-11.4, -10.0) in the Perjeta arm and -10.6 (95% -11.4, -9.9) in the placebo arm; global health status was -11.2 (95% CI -12.2, -10.2) in the Perjeta arm and -10.2 (95% CI -11.1,-9.2) in the placebo arm. Change in diarrhoea symptoms increased to +22.3 (95% CI 21.0, 23.6) in the Perjeta arm vs +9.2 (95% CI 8.2, 10.2) in the placebo arm.

Thereafter in both arms, physical function and global health status scores returned to baseline levels during targeted treatment. Diarrhoea symptoms returned to baseline after HER2 therapy in the Perjeta arm. The addition of Perjeta to Herceptin plus chemotherapy did not affect patients' overall role function over the course of the study.

Metastatic Breast Cancer

CLEOPATRA (WO20698)

CLEOPATRA is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial conducted in 808 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. Patients were randomized 1:1 to receive placebo plus Herceptin and docetaxel or Perjeta plus Herceptin and docetaxel. Randomization was stratified by prior treatment status (de novo or prior adjuvant/neoadjuvant therapy) and geographic region (Europe, North America, South America and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of at least 12 months before enrollment into the trial.

Perjeta and Herceptin were administered intravenously as outlined in Table 4. Patients were treated with Perjeta and Herceptin until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

At the time of the primary analysis, the mean number of cycles of study treatment received was 16.2 in the placebo treatment group and 19.9 in the Perjeta-treated group.

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (IRF) and defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumor assessment. Secondary efficacy endpoints were overall survival (OS), PFS (investigator-assessed), objective response rate (ORR), duration of response, and time to symptom progression according to the FACT B QoL questionnaire.

Demographics were well balanced (median age was 54 years old, the majority were Caucasian (59%) and all were female with the exception of 2 patients). Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) and approximately half of the patients in each treatment group had received prior adjuvant or neoadjuvant therapy (192 patients [47.3%] in the placebo-treated group vs 184 patients [45.8%] Perjeta-treated group).

At the time of the primary progression-free survival analysis, a total of 242 patients (59%) in the placebo-treated group and 191 patients (47.5%) in the Perjeta-treated group had IRF-confirmed progressive disease or had died within 18 weeks of their last tumor assessment.

At the time of the primary analysis the CLEOPATRA study demonstrated a statistically significant improvement in IRF-assessed PFS (hazard ratio [HR]=0.62, 95% CI=0.51, 0.75, p < 0.0001) in the Perjeta-treated group compared with the placebo-treated group, and an increase in median PFS of 6.1 months (median PFS of 12.4 months in the placebo-treated group vs 18.5 months in the Perjeta-treated group) (see *Figure 3*). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS (median PFS was 12.4 months for placebo vs 18.5 months for Perjeta) (see *Table 8*). Consistent results were observed across prespecified patient subgroups including the subgroups based on stratification factors of geographic region and prior adjuvant/neoadjuvant therapy or de novo metastatic breast cancer (see *Figure 4*).

The efficacy results from the CLEOPATRA trial are summarized in Table 8:

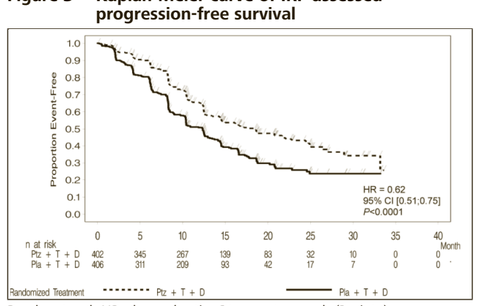
Table 8 Summary of efficacy from CLEOPATRA study

Parameter	Placebo + Herceptin + docetaxel n=406	Perjeta + Herceptin + docetaxel n=402	HR (95% CI)	p-value
Primary Endpoint: Progression-Free Survival (IRF review)				
No. of patients with an event	242 (59%)	191 (47.5%)	0.62	< 0.0001
Median months	12.4	18.5	[0.51;0.75]	
Secondary Endpoint: Overall Survival (Final analysis of OS)				
No. of patients with an event*	221 (54.4%)	168 (41.8%)	0.68	0.0002
Median months	40.8	56.5	[0.56;0.84]	
Secondary Endpoint: Progression-Free Survival (investigator assessment)				
No. of patients with an event	250 (61.6%)	201 (50.0%)	0.65	< 0.0001
Median months	12.4	18.5	[0.54;0.78]	
Secondary Endpoint: Objective Response Rate (ORR)				
No. of patients with an event				
Responders**	336	343	Difference in ORR: 10.8% [4.2,17.5]%	0.0011
95% CI for ORR	233 (69.3%)	275 (80.2%)		
Complete response (CR)	[64.1; 74.2]	[75.6; 84.3]		
Partial Response (PR)	14 (4.2%)	19 (5.5%)		
Stable disease (SD)	219 (65.2%)	256 (74.6%)		
Progressive disease (PD)	70 (20.8%)	50 (14.6%)		
	28 (8.3%)	13 (3.8%)		

Parameter	Placebo + Herceptin + docetaxel n=406	Perjeta + Herceptin + docetaxel n=402	HR (95% CI)	p-value
Duration of Response ^				
n=	233	275		
Median weeks	54.1	87.6		
95% CI for Median	[46;64]	[71;106]		

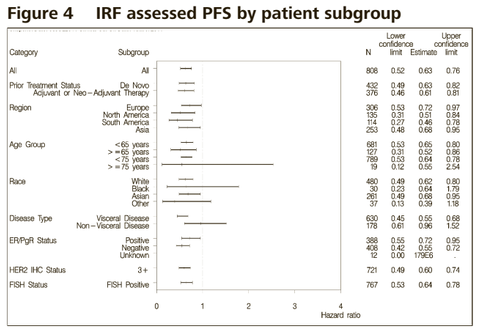
* Final analysis of overall survival, cutoff date 11 Feb 2014.
** Patients with best overall response of confirmed CR or PR by RECIST.
^ Evaluated in Patients with Best Overall Response of CR or PR.
Objective response rate and duration of response are based on IRF-assessed tumour assessments.

Figure 3 Kaplan-Meier curve of IRF-assessed progression-free survival



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab (Perjeta); T=trastuzumab (Herceptin)

Figure 4 IRF assessed PFS by patient subgroup

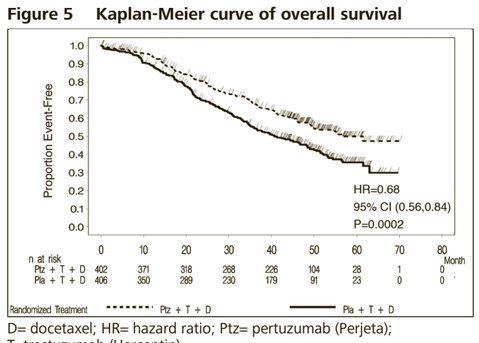


At the primary analysis of efficacy, an interim analysis of OS showed a strong trend suggestive of a survival benefit in favor of the Perjeta-treated group.

An interim analysis of OS performed one year after the primary analysis of efficacy, demonstrated a statistically significant OS benefit in favor of the Perjeta-treated group (HR 0.66, p=0.0008 log-rank test). The median time to death was 37.6 months in the placebo-treated group but had not yet been reached in the Perjeta-treated group.

The final analysis of OS was performed when 389 patients had died (221 in the placebo-treated group and 168 in the Perjeta-treated group). The statistically significant OS benefit in favor of the Perjeta-treated group was maintained (HR 0.68, p=0.0002 log-rank test). The median time to death was 40.8 months in the placebo-treated group and 56.5 months in the Perjeta-treated group (see *Table 8, Figure 5*).

Figure 5 Kaplan-Meier curve of overall survival



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab (Perjeta); T=trastuzumab (Herceptin)

There was no statistically significant difference between treatment groups in Health Related Quality of Life as assessed by time to symptom progression on the FACT-B TOI-PFB subscale, defined as a 5 point reduction in subscale score (HR=0.97, 95% CI=0.81; 1.16). In an exploratory analysis, patients treated with Perjeta in combination with Herceptin and docetaxel experienced a lower risk of symptom progression on the FACT-B breast cancer subscale (defined as a 2 point reduction in subscale score) compared to those treated with Herceptin and docetaxel alone (HR=0.78, 95% CI=0.65; 0.94).

PHranceSCa (MO40628)

Study MO40628 investigated the safety of switching from intravenous pertuzumab and trastuzumab to Phesgo (and vice versa) with a primary objective to evaluate patient preference for Phesgo. A total of 160 patients were included in this 2-arm, cross-over study: 80 patients were randomized to Arm A (3 cycles of intravenous pertuzumab and trastuzumab followed by 3 cycles of Phesgo) and 80 patients were randomized to Arm B (3 cycles of Phesgo followed by 3 cycles intravenous pertuzumab and trastuzumab). After that, patients could choose to continue their treatment with intravenous pertuzumab and trastuzumab or with Phesgo to complete a total of 18 cycles of HER2-targeted therapy.

At primary analysis, 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. 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.

Among the patients in Arm A, the incidence of AEs was similar when switching from intravenous pertuzumab and trastuzumab to Phesgo. Within Arm A, the incidence of AEs during Cycles 1-3 (IV) was 77.5% compared to Cycles 4-6 (SC) which was 72.5%. Within Arm B, the incidence of AEs during Cycles 1-3 (SC) was 77.5% compared to Cycles 4-6 (IV) which was 63.8%. The total number of events was higher during Cycles 1-3 compared to Cycles 4-6, regardless of treatment administered.

3.1.3 Immunogenicity

As with all therapeutic proteins, there is the potential for immune response in patients treated with Phesgo.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of treatment-emergent antibodies to Phesgo with the incidence of antibodies to other products may be misleading.

In the FEDERICA study, the incidence of treatment-emergent anti-pertuzumab and anti-trastuzumab antibodies was 3% (7/237) and 0.4% (1/237), respectively, in patients treated with intravenous Perjeta and Herceptin.

The incidence of treatment-emergent anti-pertuzumab, anti-trastuzumab, and anti- vorhyaluronidase alfa antibodies was 4.8% (11/231), 0.9% (2/232), and 0.9% (2/225), respectively, in patients treated with Phesgo. The clinical relevance of the development of anti-pertuzumab, anti-trastuzumab or anti-vorhyaluronidase alfa antibodies after treatment with Phesgo is unknown.

3.2 PHARMACOKINETIC PROPERTIES

Pertuzumab and trastuzumab exposure following subcutaneous administration of Phesgo (1200 mg pertuzumab/600 mg trastuzumab loading dose followed by 600 mg pertuzumab/600 mg trastuzumab every 3 weeks) in the FEDERICA study is shown in Table 4. The pharmacokinetic (PK) results for the primary endpoint of pertuzumab Cycle 7 C_{trough} (i.e. pre-dose Cycle 8), showed non-inferiority of pertuzumab within Phesgo (geometric mean 88.7 mcg/mL) compared to intravenous Perjeta (geometric mean 72.4 mcg/mL) with a geometric mean ratio of 1.22 (90% CI: 1.14–1.31). The lower boundary of the two-sided 90% confidence interval for the geometric mean ratio of pertuzumab within Phesgo and intravenous Perjeta was 1.14, i.e. greater than the predefined margin of 0.8.

The PK results for the secondary endpoint, trastuzumab Cycle 7 C_{trough} (i.e. pre-dose Cycle 8), showed non-inferiority of trastuzumab within Phesgo (geometric mean 57.5 mcg/mL) compared to intravenous trastuzumab (geometric mean 43.2 mcg/mL) with a geometric mean ratio of 1.33 (90% CI: 1.24–1.43).

A population PK model of pertuzumab with linear elimination from the central compartment was constructed using pooled pertuzumab within Phesgo and intravenous Perjeta PK data from FEDERICA to describe the observed pertuzumab PK concentrations following subcutaneous Phesgo administration and intravenous Perjeta administration.

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled trastuzumab PK data from the phase III study BO22227 (HANNAH) of subcutaneous trastuzumab vs intravenous trastuzumab, to describe the observed PK concentrations following intravenous trastuzumab or subcutaneous trastuzumab administration in HER2 positive EBC patients. The PK analysis using the HANNAH population PK model demonstrated that there was no impact on the PK of trastuzumab within Phesgo from pertuzumab within Phesgo as consistent PK were observed between trastuzumab within Phesgo and subcutaneous trastusumab.

The population PK predicted pertuzumab and trastuzumab exposures are summarized in Table 9 below.

Table 9 Pertuzumab and trastuzumab exposure (median with 5th-95th Percentiles) following subcutaneous administration of Phesgo or intravenous Perjeta or Herceptin[a]

Parameter		Pertuzumab within Phesgo	Intravenous pertuzumab	Trastuzumab within Phesgo[b]	Intravenous trastuzumab[b]
C_{trough} (mcg/mL)	Cycle 5	85.1 (48.7 – 122.5)	74.9 (47.8 - 99.8)	27.7 (13.6-43.2)	31.4 (21.1-50.9)
	Cycle 7	88.9 (51.8 - 142.5)	78.5 (41.3 - 114.9)	57.5 (27.2-92.7)	44.9 (29.7-76.2)
C_{max} (mcg/mL)	Cycle 5	106.5 (62.9 - 152.6)	304.8 (191.1- 409.7)	44.6 (31.0-63.1)	172.9 (133.7-238.9)
	Cycle 7	149.5 (88.5 - 218.5)	225.9 (158.5 - 301.8)	117.3 (72.2-166.6)	169.1 (130.6-238.9)
$AUC_{0\text{-}21\ days}$ (mcg/mL•day)	Cycle 5	2306.9 (1388.4 - 3376.2)	2519.7 (1898.4 - 3138.9)	1023.8 (634.3-1442.6)	1341.0 (1033.1-2029.0)
	Cycle 7	2569.3 (1487.4 - 3786.1)	2454.3 (1561.4 - 3346.1)	1838.7 (1024.3-2715.5)	1668.6 (1264.7- 2576.9)

[a] First dose of Phesgo, intravenous Perjeta and Herceptin administered at Cycle 5
[b] Study BO22227 HANNAH population PK model used for trastuzumab PK simulation

3.2.1 Absorption

The median maximum serum concentration (C_{max}) of pertuzumab within Phesgo and time to maximal concentration (T_{max}) were 157 ug/mL and 3.82 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.712 and the first-order absorption rate (K_a) is 0.348 (1/day).

The median maximum serum concentration (C_{max}) of trastuzumab within Phesgo and time to maximal concentration (T_{max}) were 114 ug/mL and 3.84 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.771 and the first-order absorption rate (K_a) is 0.404 (1/day).

3.2.2 Distribution

Based on population PK analysis, the volume of distribution of the central (Vc) compartment of pertuzumab within Phesgo in the typical patient, was 2.77 L.

Based on population PK analysis, the volume of distribution of the central (Vc) compartment of subcutaneous trastuzumab in the typical patient, was 2.91 L.

3.2.3 Metabolism

The metabolism of Phesgo has not been directly studied. Antibodies are cleared principally by catabolism.

3.2.4 Elimination

Based on population pharmacokinetic (PK) analysis, the clearance of pertuzumab within Phesgo was 0.163 L/day and the elimination half-life ($t_{1/2}$) was approximately 24.3 days.

Based on population pharmacokinetic (PK) analysis, the linear clearance of subcutaneous trastuzumab was 0.111 L/day. Trastuzumab is estimated to reach concentrations that are < 1 µg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) in at least 95% patients 7 months after the last dose.

Pharmacokinetics in Special Populations

Pediatric Population
No studies have been conducted to investigate the pharmacokinetics of Phesgo in the pediatric population.

Geriatric Population
No studies have been conducted to investigate the pharmacokinetics of Phesgo in geriatric patients.

In population PK analyses of pertuzumab within Phesgo and intravenous Perjeta, age was not found to significantly affect PK of pertuzumab.

In population PK analyses of subcutaneous or intravenous Herceptin, age has been shown to have no effect on the disposition of Herceptin.

Renal Impairment
No formal PK study of Phesgo has been conducted in patients with renal impairment.

Based on population PK analyses of pertuzumab within Phesgo and intravenous Perjeta, renal impairment was shown not to affect pertuzumab exposure; however, only limited data from patients with severe renal impairment were included in population PK analyses.

In a population pharmacokinetic analysis of subcutaneous and intravenous Herceptin, renal impairment was shown not to affect Herceptin disposition.

Hepatic Impairment
No formal pharmacokinetic study of Phesgo has been conducted in patients with hepatic impairment.

3.3 NONCLINICAL SAFETY

No dedicated studies were conducted with the combination of subcutaneous pertuzumab, trastuzumab, and vorhyaluronidase alfa.

Subcutaneous and Intravenous Perjeta and Herceptin

Subcutaneous pertuzumab (250 mg/kg/week for 4 weeks) and intravenous pertuzumab (up to 150 mg/kg weekly for up to 26 weeks) was well tolerated in cynomolgus monkeys (binding species), except for the development of diarrhoea. With intravenous pertuzumab doses of 15 mg/kg and higher, intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys, chronic dosing (26 weekly doses) resulted in episodes of diarrhoea-related dehydration which were managed with intravenous fluid replacement therapy. Trastuzumab was well tolerated in mice (non-binding species), rabbits (non-binding species) and Macaque (rhesus and cynomolgus) monkeys (binding species) in single-dose (IV) and repeat-dose toxicity (SC and IV) studies of up to 13 weeks (25 mg/kg twice weekly) or 26 weeks (25 mg/kg weekly) duration, respectively. No evidence of acute or chronic toxicity was identified.

Intravenous Herceptin

Lactation
A study conducted in cynomolgus monkeys that had received trastuzumab at doses 25 times that of the weekly human maintenance dose of 2 mg/kg intravenous trastuzumab from days 120 to 150 of pregnancy, demonstrated that trastuzumab is secreted in the milk postpartum. The exposure to trastuzumab in utero and the presence of trastuzumab in the serum of these infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age.

3.3.1 Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of pertuzumab or trastuzumab within Phesgo.

3.3.2 Genotoxicity

No studies have not been performed to evaluate the mutagenic potential of pertuzumab or trastuzumab within Phesgo.

3.3.3 Impairment of Fertility

Intravenous Perjeta
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 month duration in cynomolgus monkeys.

Intravenous Herceptin
Reproduction studies of female fertility have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg intravenous trastuzumab and have revealed no evidence of impaired fertility. Additionally, no adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six month duration in cynomolgus monkeys.

3.3.4 Reproductive Toxicity

Intravenous Pertuzumab
Reproductive toxicology studies have been conducted in cynomolgus monkeys at loading doses of 30 to 150 mg/kg and maintenance doses of 10 to 100 mg/kg achieving clinically relevant exposures. Intravenous administration of pertuzumab from Gestation Day (GD) 19 through 50 (period of organogenesis) has been shown to be embryotoxic with a dose dependent increase in embryo-fetal deaths between GD 25 to 70. Delayed renal development and oligohydramnios were identified at GD 100.

Intravenous Trastuzumab
Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg intravenous trastuzumab and have revealed no evidence of harm to the fetus. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) fetal development period was observed.

3.3.5 Other

Subcutaneous Trastuzumab
Subcutaneous trastuzumab with vorhyaluronidase alfa was well tolerated in a rabbit local tolerance study (non-binding species) and in a 13-week repeat dose toxicity study in cynomolgus monkeys (binding species).

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Vials
Store at 2°C-8°C.

Keep vial in the outer carton in order to protect from light.

Do not freeze.

This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

The 1200 mg pertuzumab/600 mg trastuzumab and 600 mg pertuzumab/600 mg trastuzumab solution are ready to use

11024343_02
LEAF PHESGO VIAL ID
Artworks Center - Roche Mannheim

Artworks Creator:	Perigord	25-Jun-2024	Version 1
Type size:	9 pt		
Format:	450x500 mm	folded: 47x60 mm	double PP
Drawing Norm:	NP9358	17-Aug-2010	10.115 - 3
Phoenix Norm:	spt022447	06-Jun-2014	Version 5.0
Colours:	P Black C		

solutions for injection which does not need to be mixed with other drugs or diluted.

Phesgo should be inspected visually to ensure there is no particulate matter or discolouration prior to administration. Do not shake.

Phesgo solution for injection is for single use only and should be prepared by a health care professional using aseptic technique.

From a microbiological point of view, the medicine should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative. If not used immediately, preparation should take place in controlled and validated aseptic conditions. Once transferred from the vial to the syringe, the medicinal product is physically and chemically stable for 28 days at 2°C-8°C or 24 hours at 9°C-30°C.

After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying of the solution in the needle and not compromise the quality of the medicinal product. Label the syringe with the peel-off sticker. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 10 mL (600 mg pertuzumab/600 mg trastuzumab) or 15 mL (1200 mg pertuzumab/600 mg trastuzumab).

No incompatibilities between Phesgo and polypropylene, polycarbonate, polyurethane, polyethylene, polyvinyl chloride and fluorinated ethylene polypropylene have been observed.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:
- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

4.3 PACKS

Box, 1 vial @ 1200 mg/600 mg/15 mL — Reg. No.: DKI2257511243A1

Box, 1 vial @ 600 mg/600 mg/10 mL — Reg. No.: DKI2257511243B1

Medicine: keep out of reach and sight of children
Obat: Jauhkan dari jangkauan dan pandangan anak-anak
On medical prescription only
Harus dengan resep dokter

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Made for:
F. Hoffmann-La Roche Ltd., Basel, Switzerland
by F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland

Imported by:
PT Menarini Indria Laboratories
Bekasi, Indonesia

Distributed by:
PT Roche Indonesia
Jakarta, Indonesia

INFORMASI PRODUK UNTUK PASIEN

PHESGO®

Pertuzumab and Trastuzumab

Cairan untuk injeksi subkutan
1200 mg/600 mg
600 mg/600 mg

Bacalah keseluruhan isi brosur ini dengan saksama sebelum Anda memulai menggunakan obat ini karena brosur ini memuat informasi yang penting bagi Anda.
- Simpanlah brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka serupa dengan penyakit Anda.
- Jika Anda mengalami efek samping, bicarakanlah dengan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi di luar dari apa yang tercantum pada brosur ini. Lihat bagian 4.

Apakah isi brosur ini:

1. Apa itu Phesgo dan kegunaannya

Phesgo merupakan obat kanker yang mengandung dua bahan aktif bernama pertuzumab dan trastuzumab.
- Pertuzumab dan trastuzumab adalah "antibodi monoklonal". Keduanya didesain untuk berikatan pada target tertentu pada sel tubuh yang disebut "*human epidermal growth factor receptor 2*" (HER2)."
- HER2 ditemukan dalam jumlah yang banyak pada permukaan beberapa jenis sel kanker dimana ia menstimulasi pertumbuhan sel kanker tersebut.
- Dengan berikatan dengan sel-sel kanker yang memiliki reseptor HER2, maka Phesgo akan menghambat atau menghentikan pertumbuhan sel-sel kanker tersebut atau membunuh sel-sel kanker tersebut.

Phesgo tersedia dalam dua kekuatan yang berbeda. Lihat bagian 6 untuk informasi lebih lanjut.
Phesgo digunakan untuk mengobati pasien dewasa yang menderita kanker payudara jenis "HER2-positif", dimana dokter Anda akan melakukan pemeriksaan untuk memastikan hal ini.
Phesgo dapat digunakan apabila:
- Kanker payudara tersebut telah menyebar ke bagian tubuh lainnya (telah mengalami metastasis) atau kanker payudara yang tidak dapat diangkat *(unresectable)* yang muncul kembali di payudara Anda setelah sebelumnya berhasil diterapi dengan adjuvan.
- Kanker payudara tersebut belum menyebar ke bagian tubuh lainnya (stadium dini) dan pengobatan diberikan sebelum operasi (pengobatan sebelum operasi disebut terapi neoadjuvan).
- Kanker payudara tersebut belum menyebar ke bagian tubuh lainnya (stadium dini) dan pengobatan diberikan setelah operasi jika terdapat risiko tinggi untuk kekambuhan kanker (pengobatan setelah operasi disebut terapi adjuvan).

Sebagai bagian dari terapi, Anda juga akan diberikan secara bersamaan obat-obatan yang disebut dengan kemoterapi. Informasi tentang obat-obatan ini terdapat pada brosur masing-masing. Tanyakan pada dokter, apoteker atau perawat Anda agar Anda diberikan informasi tentang obat-obatan tambahan tersebut.

2. Apa yang perlu Anda ketahui sebelum diberikan Phesgo

Anda tidak boleh diberikan Phesgo
- Jika Anda alergi terhadap pertuzumab, trastuzumab atau terhadap bahan-bahan lainnya yang terkandung di dalam obat ini (tersebut tercantum dalam bagian 6).

Jika Anda tidak yakin tentang hal ini, silakan bicarakan dengan dokter, apoteker atau perawat Anda sebelum Anda diberikan Phesgo.

Peringatan dan Perhatian

Gangguan pada Jantung
Pemberian Phesgo dapat memengaruhi jantung. Silakan berkonsultasi dengan dokter, apoteker atau perawat Anda sebelum Anda diberikan Phesgo apabila:
- Anda pernah mengalami gangguan jantung (seperti gagal jantung, terapi untuk detak jantung tidak beraturan yang serius, tekanan darah tinggi yang tidak terkontrol, serangan jantung baru-baru ini). Dokter Anda akan melakukan pemeriksaan untuk mengetahui apakah jantung Anda bekerja dengan baik sebelum dan selama pemberian Phesgo.
- Anda pernah mengalami gangguan jantung pada terapi sebelumnya dengan menggunakan Herceptin.
- Anda pernah diberikan obat kemoterapi dari kelas yang disebut sebagai antrasiklin, misalnya *doxorubicin* atau *epirubicin*–obat-obatan ini dapat merusak otot jantung serta akan meningkatkan risiko terjadinya gangguan jantung pada saat menggunakan Phesgo.
- Anda melakukan radioterapi pada area dada sebelum mendapatkan pengobatan Phesgo karena hal tersebut dapat meningkatkan risiko gangguan pada jantung.

Jika ada di antara hal-hal tersebut di atas yang terjadi pada diri Anda (atau jika Anda tidak yakin), sebaiknya Anda berkonsultasi dengan dokter, apoteker atau perawat Anda sebelum Anda diberikan Phesgo. Silakan baca bagian 4 'Efek samping serius' untuk memperoleh keterangan lebih lanjut terkait tanda-tanda adanya gangguan pada jantung yang perlu diperhatikan.

Reaksi terkait Injeksi
Reaksi yang terkait dengan injeksi dapat terjadi. Reaksi tersebut adalah alergi dan dapat sangat berat. Dokter, apoteker atau perawat Anda akan melihat apakah terjadi efek samping selama pemberian injeksi Anda pada rentang waktu:
- 30 setelah pemberian injeksi pertama Phesgo
- 15 menit setelah pemberian injeksi Phesgo berikutnya

Jika Anda mengalami suatu reaksi yang serius, maka dokter Anda mungkin akan menghentikan pengobatan dengan Phesgo.

Febrile Neutropenia (penurunan jumlah sel darah putih (neutrofil) dalam darah disertai demam)
Ketika Phesgo diberikan bersama-sama dengan terapi kanker lainnya yaitu kemoterapi, ada kemungkinan jumlah sel darah putih dalam darah Anda akan turun dan Anda akan mengalami demam (suhu tubuh naik). Jika saluran pencernaan Anda mengalami peradangan (misalnya: sakit pada rongga mulut atau diare), maka kemungkinan Anda akan mengalami efek samping ini menjadi lebih besar. Jika demam berlangsung selama beberapa hari, ini mungkin merupakan tanda pemburukan kondisi Anda dan Anda harus menghubungi dokter.

Diare
Pengobatan dengan Phesgo dapat menyebabkan diare yang berat. Pasien dengan usia lanjut (lebih dari 65 tahun) lebih rentan mengalami diare dibandingkan dengan pasien di bawah usia 65 tahun. Jika Anda mengalami diare yang berat ketika menerima pengobatan antikanker, dokter Anda dapat memberikan obat antidiare untuk mengatasi diare selama terapi. Dokter Anda juga dapat menghentikan pengobatan Anda dengan Phesgo hingga diare terkontrol.

Penggunaan pada anak-anak dan remaja
Phesgo tidak diperkenankan untuk digunakan pada pasien dengan usia di bawah 18 tahun, karena masih belum ada informasi tentang bagaimana efek kerja obat ini pada kelompok usia tersebut.

Penggunaan pada pasien dengan usia lanjut
Pasien di atas usia 65 tahun lebih sering mengalami efek samping seperti berkurangnya nafsu makan, menurunnya jumlah sel darah merah, berat badan turun, kelelahan, hilangnya atau berubahnya pengecap, kelemahan, mati rasa, sensasi kesemutan atau tertusuk yang terutama menyerang kaki dan tungkai serta diare, dibandingkan dengan pasien dibawah usia 65 tahun.

Obat-obatan lain dan Phesgo
Beri tahu dokter, apoteker atau perawat Anda apabila Anda sedang, baru saja, atau akan menggunakan obat-obat lainnya juga. Ini termasuk obat-obatan tanpa resep serta obat-obatan herbal.

Kehamilan, menyusui dan kontrasepsi
Sebelum memulai penggunaan obat ini, Anda harus memberi tahu dokter, apoteker atau perawat Anda bahwa Anda sedang hamil atau sedang menyusui, atau ada kemungkinan bahwa Anda sedang hamil atau berencana untuk hamil. Dokter, apoteker atau perawat Anda akan memberi tahu Anda segala manfaat dan risiko bagi Anda dan bayi Anda apabila Anda menggunakan Phesgo pada saat masa kehamilan.
- Segeralah memberi tahu dokter Anda apabila tiba-tiba Anda hamil selama masa pengobatan menggunakan Phesgo atau selama rentang waktu 7 bulan setelah selesainya masa pengobatan. Penggunaan Phesgo dapat membahayakan janin. Oleh karena itu Anda harus menggunakan alat kontrasepsi yang efektif selama terapi Phesgo ini serta pada rentang waktu 7 bulan setelah selesainya terapi.
- Tanyakan pada dokter Anda apakah Anda boleh menyusui selama atau setelah masa pengobatan dengan Phesgo.

Mengemudi dan mengoperasikan mesin
Phesgo mungkin dapat memengaruhi kemampuan Anda untuk mengemudi atau mengoperasikan mesin. Jika Anda merasa pusing, dingin, demam, atau terdapat reaksi terkait injeksi atau reaksi alergi seperti dijelaskan di bagian 4 di bawah, maka tunggulah sampai semua reaksi itu hilang sebelum Anda mengemudi atau mengoperasikan mesin.

Phesgo mengandung natrium
Phesgo mengandung < 1 mmol natrium (23 mg) per dosis, maka dapat dinyatakan "tidak mengandung natrium/*sodium free*".

3. Cara penggunaan Phesgo

Penggunaan obat Phesgo
Terapi Phesgo dilaksanakan oleh dokter, apoteker atau perawat di rumah sakit atau klinik dengan cara penyuntikan atau injeksi di bawah kulit Anda (injeksi subkutan)
- Injeksi akan diberikan setiap tiga minggu.
- Anda akan diberikan injeksi pertama pada bagian paha dan injeksi berikutnya di bagian paha lainnya. Titik suntik harus bergantian antara paha kiri dan paha kanan.
- Dokter atau perawat Anda akan memastikan setiap penyuntikan dilakukan di titik suntik baru (berjarak sekurang-kurangnya 2,5 cm dari titik suntik lama), dan dimana area kulit tersebut tidak memerah, memar, lunak, atau keras.
- Jika akan memberikan obat lain secara subkutan selama terapi Phesgo, maka harus menggunakan titik suntik yang berbeda.

Untuk injeksi pertama (dosis awal)
- Phesgo 1200 mg/600 mg akan diberikan secara injeksi di bawah kulit Anda selama 8 menit. Dokter, apoteker atau perawat Anda akan melihat apakah terjadi efek samping selama pemberian injeksi hingga rentang waktu 30 menit setelahnya.
- Anda juga akan diberikan obat kemoterapi lainnya.

Untuk injeksi berikutnya (dosis pemeliharaan), akan diberikan jika injeksi pertama berhasil diterima oleh tubuh dengan baik:
- Phesgo 600 mg/600 mg akan diberikan secara injeksi di bawah kulit Anda selama 5 menit. Dokter, apoteker atau perawat Anda akan melihat apakah terjadi efek samping selama pemberian injeksi hingga rentang waktu 15 menit setelahnya.
- Anda juga akan diberikan obat kemoterapi lainnya, sesuai resep dokter.
- Jumlah suntikan yang diberikan kepada Anda bergantung pada:
  - respons tubuh Anda terhadap terapi
  - apakah Anda pernah mendapatkan terapi lain sebelum dioperasi (terapi neoadjuvan) atau setelah operasi (terapi adjuvan) atau untuk penyakit yang sudah menyebar.

Informasi lebih lanjut mengenai dosis awal dan dosis pemeliharaan dapat dilihat pada bagian 6.
Untuk memperoleh penjelasan lebih lanjut terkait dosis kemoterapi (harap diperhatikan bahwa kemoterapi juga dapat menimbulkan efek samping), silakan baca brosur pada kemasan produk tersebut untuk dapat memahami tujuan penggunaannya. Jika masih ada hal-hal yang ingin ditanyakan tentang obat-obatan ini, silakan bertanya kepada dokter, apoteker atau perawat Anda.

Jika Anda lupa untuk mendapatkan terapi Phesgo
Jika Anda lupa atau terkendala untuk datang dan mendapatkan pengobatan Phesgo, maka segeralah membuat jadwal pemberian yang baru sesegera mungkin. Dosis yang diberikan oleh dokter bergantung pada berapa lama jeda waktu semenjak terakhir kali Anda menjalani terapi.

Jika Anda menghentikan terapi Phesgo
Anda tidak diperkenankan untuk menghentikan terapi Phesgo ini tanpa berkonsultasi dengan dokter Anda sebelumnya. Penting bagi Anda untuk mendapatkan keseluruhan dosis injeksi yang telah direkomendasikan untuk Anda tepat waktu setiap tiga minggu. Hal ini membuat obat dapat bekerja dengan baik.

Jika masih ada hal-hal yang ingin ditanyakan tentang penggunaan obat ini, silakan bertanya kepada dokter, apoteker atau perawat Anda.

4. Efek samping yang mungkin terjadi

Sebagaimana halnya dengan obat-obatan lainnya, obat Phesgo ini juga dapat menyebabkan efek samping, meskipun tidak semua pasien mengalaminya.

Efek samping serius

Segeralah memberi tahu dokter, apoteker atau perawat Anda apabila Anda mengetahui munculnya efek samping sebagai berikut:
- **Gangguan jantung:** jantung berdetak lebih lambat atau cepat dari biasanya atau jantung berdebar dengan gejala yang menyertai berupa batuk, sulit bernapas, serta pembengkakan (retensi cairan tubuh) pada kaki atau lengan Anda.
- **Reaksi alergi terkait injeksi:** dapat berupa reaksi alergi ringan atau berat dan termasuk rasa sakit, demam, menggigil, rasa lelah, sakit kepala, kehilangan nafsu makan, nyeri sendi dan otot, dan rasa panas.
- **Diare:** dapat berupa diare ringan atau sedang namun dapat pula sangat parah atau terus menerus 7 kali atau lebih buang air besar per hari.
- **Penurunan jumlah sel darah putih atau rendahnya jumlah sel darah putih** yang diketahui melalui tes darah dengan atau tanpa demam.
- **Reaksi alergi:** dapat berupa pembengkakan pada wajah dan tenggorokan, disertai kesulitan bernapas, kemungkinan ini merupakan gejala reaksi alergi yang serius.
- **Sindrom lisis tumor** (kondisi dimana sel kanker mati dengan cepat). Gejalanya meliputi:
  - masalah pada ginjal (kelemahan, napas pendek, lemah dan kebingungan),
  - masalah pada jantung (jantung berdebar lebih cepat atau lebih lambat),
  - kejang, muntah atau diare dan kesemutan pada mulut, tangan dan kaki.

Segeralah beri tahu dokter, apoteker atau perawat Anda apabila Anda mengamati atau merasakan munculnya efek samping seperti tersebut di atas.

Efek samping lain-lain mencakup:

Sangat umum (terjadi pada lebih dari 1 dari setiap 10 pasien):
- Penurunan jumlah neutrofil dalam darah
- Penurunan jumlah sel darah merah
- Penurunan jumlah sel darah putih
- Penurunan jumlah sel darah putih (neutrophil) dalam darah disertai demam *(febrile neutropenia)*
- Produksi air mata berlebih
- Diare
- Mual
- Muntah
- Seriawan
- Sembelit
- Nyeri pada perut bagian atas (dispepsia)
- Nyeri pada perut
- Lelah
- Inflamasi pada mukosa
- Lemas
- Demam
- Pembengkakan pada bagian tubuh seperti tangan atau tungkai/kaki
- Reaksi pada area injeksi
- Peradangan pada hidung atau tenggorokan (nasofaringitis)
- Berkurangnya nafsu makan
- Nyeri sendi
- Nyeri otot
- Nyeri pada tungkai dan sendi
- Gangguan indera pengecap/lidah (disgesia)
- Sakit kepala
- Neuropati (gangguan pada sistem saraf) sensorik tepi
- Gangguan pada sistem saraf tepi (neuropati saraf tepi)
- Pusing
- Mati rasa
- Sulit tidur
- Mimisan
- Batuk
- Sesak nafas
- Kerontokan rambut
- Ruam
- Kelainan pada kuku
- Kulit gatal
- Kulit kering
- Kulit kemerahan dan terasa panas

Umum (dapat terjadi pada hingga 1 dari 10 pasien):
- Suatu kondisi dimana ventrikel jantung sebelah kiri mengalami gangguan fungsional, baik disertai gejala atau tanpa gejala
- Hipersensitivitas
- Hipersensitivitas obat
- Infeksi saluran pernapasan bagian atas
- Radang pada bagian kulit di bawah kuku di titik pertemuan antara kuku dan kulit

Tidak umum (dapat terjadi pada hingga 1 dari setiap 100 pasien):
- Gangguan jantung kongestif
- Adanya penumpukan cairan pada paru-paru yang menyebabkan kesulitan bernapas

Jika Anda mengalami salah satu dari efek samping di atas, segera bicarakan hal tersebut kepada dokter, apoteker atau perawat Anda.

Jika Anda mengalami gejala-gejala efek samping seperti tersebut di atas setelah terapi Phesgo dihentikan, maka Anda harus dengan segera berkonsultasi dengan dokter Anda dan memberitahukan bahwa Anda sebelumnya pernah diterapi dengan menggunakan Phesgo.

Beberapa efek samping yang Anda alami bisa jadi disebabkan oleh kanker payudara Anda. Jika Anda diberikan pengobatan Phesgo dengan kemoterapi secara bersamaan, maka efek samping yang muncul bisa juga disebabkan oleh obat lain tersebut.

Pelaporan efek samping
Jika Anda mengalami efek samping apapun, konsultasikanlah dengan dokter, apoteker atau perawat Anda. Hal ini termasuk semua efek samping lainnya yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi tambahan terkait keamanan obat ini.

Anda juga dapat melaporkan efek samping secara langsung melalui:

PT Roche Indonesia–Local Safety Unit
Email: indonesia.safety@roche.com

Pusat Farmakovigilans
c.q. Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekusor dan Zat Adiktif
Badan Pengawas Obat dan Makanan Republik Indonesia
Melalui pos: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Tel: +62-21-4244691 Ext. 1079
Website: https://e-meso.pom.go.id/

5. Cara penyimpanan Phesgo

Penyimpanan Phesgo dilakukan oleh tenaga kesehatan di rumah sakit atau klinik. Rincian cara penyimpanan obat adalah sebagai berikut:
- Simpanlah obat ini jauh dari pandangan dan jangkauan anak-anak
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada kemasan luarnya (dus) setelah kata EXP. Tanggal kedaluwarsa adalah hari terakhir pada bulan yang bersangkutan.
- Simpanlah di dalam lemari pendingin (2°C-8°C).
- Jangan dibekukan.
- Simpanlah obat di dalam kemasan luarnya, untuk melindunginya dari cahaya.
- Apabila vial sudah dibuka, segera gunakan cairan injeksi tersebut. Jangan menggunakan obat ini apabila Anda melihat adanya partikel (butiran) di dalam cairan atau jika warnanya telah berubah (silakan baca bagian 6).
- Sisa obat yang tidak terpakai jangan dibuang sembarangan melalui saluran pembuangan air atau sampah rumah tangga. Tanyakan kepada apoteker Anda tentang cara membuang sisa obat-obatan yang tidak terpakai. Cara ini akan membantu menjaga lingkungan.

6. Isi dalam kemasan dan informasi lainnya

Apa sajakah yang terkandung di dalam Phesgo
Bahan aktifnya adalah pertuzumab dan trastuzumab.
- **Dosis awal:** 1 vial berisi 15 mL cairan yang mengandung 1200 mg pertuzumab dan 600 mg trastuzumab. Setiap mL mengandung 80 mg pertuzumab dan 40 mg trastuzumab.
- **Dosis pemeliharaan:** 1 vial berisi 10 mL cairan yang mengandung 600 mg pertuzumab dan 600 mg trastuzumab. Setiap mL mengandung 60 mg pertuzumab dan 60 mg trastuzumab.

Bahan-bahan lainnya adalah *vorhyaluronudase alfa*, L-histidine, L-histidine hidroklorida monohidrat, α,α trehalose dihidrat, sukrosa, L-metionin, polisorbat 20 dan air untuk injeksi (lihat bagian 2 *"Phesgo mengandung natrium"*).

Tampilan dari Phesgo serta isi dalam kemasan
Phesgo adalah cairan untuk injeksi subkutan. Cairannya jernih atau sedikit kabur menyerupai mutiara (opal), dan tidak berwarna atau sedikit coklat. Setiap kemasan berisi satu vial masing-masing berisi cairan 10 mL atau 15 mL.

Kemasan

Dus, 1 vial @ 1200 mg/600 mg/15 mL — Reg. No: DKI2257511243A1

Dus, 1 vial @ 600 mg/600 mg/10 mL — Reg. No: DKI2257511243B1

Obat: Jauhkan dari jangkauan dan pandangan anak-anak
Harus dengan resep dokter

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

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