Phesgo®

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "*Undesirable effects*" section for advice on the reporting of adverse reactions.

Phesgo®

Composition

Active substances
Pertuzumab, trastuzumab (produced by recombinant DNA technology using CHO [Chinese hamster ovary] cells).

Excipients
Human hyaluronidase (rHuPH20) (produced by recombinant DNA technology using CHO [Chinese hamster ovary] cells), L-histidine hydrochloride monohydrate, L-histidine, α,α-trehalose dihydrate, sucrose, polysorbate 20*, L-methionine, water for injection.

* produced from genetically modified maize

Pharmaceutical form and active substance quantity per unit

Solution for injection (for subcutaneous use)

1200 mg pertuzumab/600 mg trastuzumab/15 ml solution in a vial

600 mg pertuzumab/600 mg trastuzumab/10 ml solution in a vial

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

Indications/Uses

Metastatic breast cancer
Phesgo is indicated in combination with docetaxel for the treatment of patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received prior chemotherapy for their metastatic disease.

Early breast cancer
Phesgo is indicated in combination with docetaxel for neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory breast cancer or early breast cancer at high risk of recurrence (tumour size >2 cm diameter or lymph node involvement) as part of a treatment regimen for early breast cancer.

Phesgo is indicated in combination with chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (see "*Clinical efficacy*" section under "*Properties/Effects*").

Dosage/Administration

It is essential that Phesgo therapy be initiated under the supervision of a physician experienced in the treatment of cancer patients.

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Patients currently receiving intravenous pertuzumab and trastuzumab can be switched to Phesgo. The switch from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa) was investigated in study MO40628 (see "*Undesirable effects*" and "*Clinical efficacy*").

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

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

Patients treated with Phesgo should have HER2-positive tumour status, defined as an immunohistochemistry score (IHC) of 3+ or a ratio of ≥2.0 by in situ hybridisation (ISH), assessed by a validated test.

To ensure accurate and reproducible results, the tests must be performed in a specialised laboratory that can ensure validation of the test procedures.

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

Usual dosage

Metastatic and early breast cancer
For Phesgo dose recommendations in early and metastatic breast cancer, please refer to Table 1.

Table 1: Phesgo recommended dosing and administration

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

[a] Patients should be observed for injection-related reactions and hypersensitivity reactions.
[b] The observation period should start after Phesgo administration and be completed before the next administration of chemotherapy.

The injection should be alternated between the left and right thigh only. New injections should be administered at least 2.5 cm from the previous site into healthy skin and never into areas where the skin is red, bruised, tender or hard. Do not split the dose between two syringes or two injection sites. During the treatment cycle with Phesgo, other subcutaneously administered drugs should preferably be injected at different sites.

Switching from intravenous pertuzumab and trastuzumab to Phesgo
Patients given intravenous pertuzumab and trastuzumab who received the last dose <6 weeks ago should be given Phesgo as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab and every 3 weeks thereafter. Patients given intravenous pertuzumab and trastuzumab who received the last dose ≥6 weeks ago should be given Phesgo as a loading dose of 1200 mg pertuzumab/600 mg trastuzumab and then every 3 weeks as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab.

Patients treated with a taxane should be given Phesgo before 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 only be administered after completion of the entire anthracycline regimen.

Duration of treatment

Early breast cancer (EBC)
In the neoadjuvant setting (before surgery), it is recommended that patients be treated with Phesgo over three to six cycles (depending on which regimen is chosen in combination with chemotherapy) (see "*Clinical efficacy*").

In the adjuvant setting (after surgery), Phesgo should be administered for a total of one year (up to 18 cycles or until disease recurrence or unmanageable toxicity, whichever occurs first), as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. Treatment with Phesgo should start on day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see "*Clinical efficacy*").

Patients starting treatment with Phesgo in the neoadjuvant setting should continue to receive adjuvant Phesgo for a total of 1 year (up to 18 cycles) of treatment.

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.

Dose adjustment following undesirable effects/interactions
Dose reduction of Phesgo is not recommended.

For chemotherapy dose modifications, see the relevant prescribing information.

Injection-related reactions
The injection should be given more slowly or paused if the patient experiences injection-related symptoms (see "*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 "*Warnings and precautions*").

Left ventricular dysfunction
See "*Warnings and precautions*" for dose recommendations in the event of left ventricular dysfunction.

Special dosage instructions

Patients with hepatic impairment
The safety and efficacy of Phesgo have not been studied in patients with hepatic impairment. No dose recommendations can be made for Phesgo (see "*Kinetics in specific patient groups*").

Patients with 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 "*Kinetics in specific patient groups*").

Elderly patients
Dose adjustments of Phesgo are not needed in patients ≥65 years of age, although the relevant database is limited to 26 patients (see "*Safety and efficacy in elderly patients*" and "*Kinetics in specific patient groups*").

Children and adolescents
The safety and efficacy of Phesgo have not been studied in children and adolescents (<18 years of age).

Delayed administration
If the interval between two consecutive doses is less than 6 weeks, the Phesgo maintenance dose of 600 mg pertuzumab/600 mg trastuzumab should be administered as soon as possible. Do not wait until the next scheduled dose.

If the interval between two consecutive doses is 6 weeks or more, the loading dose of 1200 mg pertuzumab/600 mg trastuzumab should be readministered, followed by the maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks.

Contraindications

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

Warnings and precautions

Left ventricular dysfunction
Decreases in left ventricular ejection fraction (LVEF) have been reported with agents 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 pertuzumab in combination with trastuzumab and chemotherapy than in those treated with trastuzumab and chemotherapy. In the adjuvant setting, most cases of symptomatic heart failure occurred in patients receiving anthracycline-based chemotherapy (see "*Undesirable effects*"). Studies with intravenous pertuzumab in combination with trastuzumab and chemotherapy suggest that patients who have previously received anthracyclines or radiotherapy to the chest area may be at higher risk of decreased LVEF.

Phesgo and/or intravenous pertuzumab and trastuzumab have not been studied in patients with a pretreatment LVEF 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 or serious cardiac arrhythmia requiring treatment, or in those with cumulative prior anthracycline exposure to >360 mg/m^2 of doxorubicin or a corresponding dose of its equivalent. Intravenous pertuzumab in combination with trastuzumab and chemotherapy has not been studied in patients experiencing a decrease in LVEF to <50% during prior trastuzumab adjuvant therapy.

LVEF should be monitored before starting Phesgo and at regular intervals during treatment to ensure that it is within normal limits (see Table 2 below). If LVEF has declined as indicated in Table 2 and has not improved or has declined further at the next assessment, urgent consideration should be given to discontinuing Phesgo, unless the benefits to the individual patient are deemed to outweigh the risks.

Table 2: Dose recommendation for left ventricular dysfunction

	Pretreatment LVEF:	Monitor LVEF every:	Withhold Phesgo for at least 3 weeks if LVEF decreases to:		Resume Phesgo after 3 weeks if LVEF recovers to:	
Metastatic breast cancer[a]	≥50%	~12 weeks	Either		Either	
			<40%	40%-45% with a fall of ≥10% points below pretreatment value	>45%	40%-45% with a fall of <10% points below pretreatment value
Early breast cancer	≥55%[b]	~12 weeks (once in neoadjuvant setting)	<50% with a fall of ≥10% points below pretreatment value		Either	
					≥50%	<10% points below pretreatment value

[a] Based on data on intravenous pertuzumab use (CLEOPATRA trial).
[b] Patients treated with anthracycline-based chemotherapy require an LVEF of ≥50% on completing anthracycline therapy before starting treatment with Phesgo.

Injection/infusion-related reactions (IRRs)
Phesgo has been associated with injection-related reactions. Injection-related reactions were defined as any systemic reaction with symptoms such as fever, chills, headache, probably due to release of cytokines within 24 hours of Phesgo administration. Close observation of the patient is recommended during and for 30 minutes after administration of the loading dose and during and for 15 minutes after administration of the maintenance dose of Phesgo. If a significant injection-related reaction occurs, the injection should be given more slowly or paused, and appropriate medical therapies should be implemented. Patients should be evaluated and carefully monitored until the signs and symptoms have completely resolved. Permanent discontinuation of treatment should be considered in patients with severe injection-related reactions. The corresponding clinical assessment should be based on the severity of the preceding reaction and response to the treatment administered for the adverse reaction (see "*Dosage/Administration*"). While cases with fatal outcome due to injection-related reactions have not been observed after Phesgo administration, caution is nevertheless required as fatal infusion related-reactions have been associated with intravenous pertuzumab in combination with intravenous trastuzumab and chemotherapy.

Hypersensitivity reactions/anaphylaxis
Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and fatal events, have not been observed in patients receiving treatment with Phesgo, caution is nevertheless required as intravenous pertuzumab in combination with trastuzumab and chemotherapy has been associated with such reactions (see "*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 any of the excipients (see "*Contraindications*").

Pulmonary reactions
Severe pulmonary undesirable effects have been reported with the use of trastuzumab in the post-marketing phase (see "*Undesirable effects*"). Some of these cases have been fatal and may occur as part of an infusion-related reaction or with a delayed onset. In addition, cases of interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory failure have been reported.

Risk factors associated with interstitial lung disease include prior or concomitant administration of other anti-neoplastic therapies known to be associated with interstitial lung disease such as taxanes, gemcitabine, vinorelbine and radiotherapy. Patients experiencing dyspnoea 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.

Febrile neutropenia
Patients treated with pertuzumab, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared to patients treated with placebo, trastuzumab and docetaxel, especially during the first 3 cycles of treatment (see "*Undesirable effects*"); caution is therefore required when using Phesgo. In the CLEOPATRA trial in metastatic breast cancer, nadir neutrophil counts were similar in pertuzumab-treated and placebo-treated patients. The higher incidence of febrile neutropenia in pertuzumab-treated patients was associated with a higher incidence of mucositis and diarrhoea. Symptomatic treatment of mucositis and diarrhoea should be considered. No events of febrile neutropenia were reported after cessation of docetaxel.

Diarrhoea
Phesgo may cause severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. 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 the case of severe or prolonged diarrhoea. Interruption of treatment with Phesgo should be considered if no improvement of the condition is achieved. Once the diarrhoea has been effectively treated, treatment with Phesgo may be resumed.

Interactions

No formal drug interaction studies have been performed.

Intravenous pertuzumab
A substudy in 37 patients performed as part of the CLEOPATRA pivotal trial provided no evidence of drug interactions between pertuzumab and trastuzumab or between pertuzumab and docetaxel. In addition, population pharmacokinetic analysis identified no clinically relevant pharmacokinetic interaction between coadministered docetaxel or trastuzumab and pertuzumab. This absence of drug-drug interactions was confirmed by pharmacokinetic data from the NEOSPHERE and APHINITY studies.

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

Intravenous trastuzumab
No formal drug interaction studies have been performed with trastuzumab in humans. No clinically meaningful interactions have been observed between trastuzumab and the comedications used in clinical trials.

In studies where trastuzumab was administered in combination with docetaxel, carboplatin or anastrozole, there was no change in the pharmacokinetics of either these drugs or trastuzumab.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α-hydroxylpaclitaxel [POH] and doxorubicinol [DOL]) were not altered in the presence of trastuzumab. However, trastuzumab 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 are unclear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin.

The results of a drug interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab suggested that 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 trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggest that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

Pregnancy, lactation

Contraception
Women of childbearing potential, including female partners of male patients, should use an effective method of contraception during treatment with Phesgo and for 7 months after the last dose of Phesgo.

Pregnancy
No clinical studies have been conducted with Phesgo in pregnant women. In the post-marketing setting, 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 with trastuzumab in pregnant women. Animal studies have shown reproductive toxicity and placental transfer of trastuzumab (see "*Preclinical data*"). Phesgo should not be used during pregnancy unless clearly necessary because the potential benefit for the mother outweighs the possible risk to the fetus.

Phesgo contains recombinant human hyaluronidase (rHuPH20). For the possible impact of rHuPH20 on reproductive parameters and embryonic development in animals, see "*Preclinical data*". The impact of neutralising antibodies to rHuPH20 or endogenous hyaluronidase on reproductive parameters is unknown.

Based on post-marketing data and animal studies, Phesgo may harm the unborn child if used in 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 advisable.

Lactation
It is not known whether Phesgo is secreted in human milk. Animal studies have shown that trastuzumab is secreted in the milk (see "*Preclinical data*"). There are no data for pertuzumab. As human IgG is secreted in human milk and the potential for absorption by, and harm to, the breast-fed infant is unknown, women should be advised not to breast-feed during treatment with Phesgo and for 7 months after the last dose of Phesgo.

Fertility
No clinical data are available on fertility with Phesgo. Animal studies have revealed no evidence of impaired fertility with pertuzumab or trastuzumab (see "*Preclinical data*").

Effects on 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 "*Warnings and precautions*" and "*Undesirable effects*").

Undesirable effects

Summary of the safety profile
The safety profile of Phesgo is based on data from the phase III FEDERICA study, in which patients with HER2-positive breast cancer were treated with either Phesgo (n=248) or intravenous pertuzumab and trastuzumab (n=252) in combination with chemotherapy.

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

The most common (≥1%) serious adverse events (SAEs) in patients treated with Phesgo or intravenous pertuzumab in combination with trastuzumab were febrile neutropenia, pyrexia, neutropenia/neutrophil count decreased, neutropenic sepsis and infusion-related reactions. The SAEs were equally distributed between the Phesgo treatment arm and the treatment arm with intravenous pertuzumab in combination with trastuzumab. The following adverse drug reactions were reported more frequently (≥5%) with use of Phesgo compared to intravenous pertuzumab in combination with trastuzumab: alopecia 77% *vs* 70.2%, dyspnoea 10.1% *vs* 4.4% and fatigue 27.8% *vs* 22.6%.

Tabulated list of adverse drug reactions
The safety profile of Phesgo was consistent overall with the known safety profile of intravenous pertuzumab in combination with trastuzumab and chemotherapy from the following pivotal studies (n=3344) of treatment with pertuzumab and trastuzumab:

- CLEOPATRA, in which patients with MBC received pertuzumab in combination with trastuzumab and docetaxel (n=453).
- NEOSPHERE (n=309) and TRYPHAENA (n=218), in which patients with locally advanced, inflammatory breast cancer or EBC received neoadjuvant pertuzumab in combination with trastuzumab and chemotherapy.
- APHINITY, in which patients with EBC received adjuvant pertuzumab in combination with trastuzumab and anthracycline-based or non-anthracycline-based, taxane-containing chemotherapy (n=2364).

ADRs reported in association with the use of pertuzumab, trastuzumab and chemotherapy in the pivotal clinical trials and in the post-marketing setting are listed below.

As pertuzumab/trastuzumab is used in combination with chemotherapy, it is difficult to establish a causal relationship between an adverse reaction and a particular active substance.

The following frequency categories have been used in this section: "very common" (≥1/10), "common" (≥1/100 to <1/10), "uncommon" (≥1/1000 to <1/100), "rare" (≥1/10,000 to <1/1000), "very rare" (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing severity.

The following adverse drug reactions were reported in the pivotal trials with pertuzumab, trastuzumab and in the post-marketing setting [a,b,c]

Infections and infestations
Very common: Nasopharyngitis (12.8% [grade 3-4 <0.1%]).
Common: Upper respiratory tract infection, paronychia.

Blood and lymphatic system disorders
Very common: Neutropenia (31.4% [grade 3-4 24.2%]), anaemia (24.8% [grade 3-4 5.7%]), febrile neutropenia[d] (11.9% [grade 3-4 11.8%]), leukopenia (10.8% [grade 3-4 6.1%]).

Immune system disorders
Common: Hypersensitivity, drug hypersensitivity.

Metabolism and nutrition disorders
Very common: Decreased appetite (23.1% [grade 3-4 0.8%]).
Not known: Tumour lysis syndrome[g].

Psychiatric disorders
Very common: Insomnia (15.9% [grade 3-4 0.2%]).

Nervous system disorders
Very common: Dysgeusia (22.7% [grade 3-4 <0.1%]), headache (21.8% [grade 3-4 0.4%]), peripheral sensory neuropathy (15.7% [grade 3-4 0.5%]), neuropathy peripheral (14.7% [grade 3-4 0.7%]), dizziness (11.2% [grade 3-4 0.1%]), paraesthesia (10.2% [grade 3-4 0.4%]).

Eye disorders
Very common: Lacrimation increased (12.1%).

Cardiac disorders
Common: Left ventricular dysfunction[e].
Uncommon: Cardiac failure congestive[e].

Respiratory, thoracic and mediastinal disorders
Very common: Epistaxis (15.6% [grade 3-4 <0.1%]), cough (15.5% [grade 3-4 <0.1%]), dyspnoea (11.5% [grade 3-4 0.5%]).
Uncommon: Pleural effusion.

Gastrointestinal disorders
Very common: Diarrhoea (67.9% [grade 3-4 8.9%]), nausea (60.8% [grade 3-4 1.9%]), vomiting (30.0% [grade 3-4 1.7%]), stomatitis (24.9% [grade 3-4 1.6%]), constipation (24.5% (grade 3-4 0.4%]), dyspepsia (13.2% [grade 3-4 <0.1%]), abdominal pain (11.7% [grade 3-4 0.4%]).

Skin and subcutaneous tissue disorders
Very common: Alopecia (63.1% [grade 3-4 <0.1%]), rash (26.4% [grade 3-4 0.5%]), nail disorders (12.9% [grade 3-4 0.3%]), pruritus (12.9% [grade 3-4 <0.1%]), dry skin (11.7% [grade 3-4 <0.1%]).

Musculoskeletal and connective tissue disorders
Very common: Arthralgia (24.6% [grade 3-4 0.7%]), myalgia (24.3% [grade 3-4 0.8%]), pain in extremity (10.0% [grade 3-4 0.2%]).

General disorders and administration site conditions
Very common: Fatigue (44.3% [grade 3-4 3.3%]), mucosal inflammation (23.2% [grade 3-4 1.5%]), asthenia (20.9% [grade 3-4 1.5%]), pyrexia (18.9% [grade 3-4 0.6%]), oedema peripheral (16.2% [grade 3-4 <0.1%]), injection site reactions (12.9%, grade 3-4: 0%)[f].

Vascular disorders
Very common: Hot flush (15.7% [grade 3-4 0.1%]).

[a] Pooled data from the overall treatment period in CLEOPATRA; from the neoadjuvant treatment period in NEOSPHERE and TRYPHAENA; and from the treatment period in APHINITY. In addition, ADRs are listed that are specific to the Phesgo route of administration and have been reported in the FEDERICA study.
[b] In NEOSPHERE, 108 patients received only pertuzumab + trastuzumab without docetaxel, and 94 patients received pertuzumab + docetaxel without trastuzumab.
[c] In CLEOPATRA, 45 patients who had received placebo after randomisation and had not been previously treated with pertuzumab switched to treatment with pertuzumab and are included in the figure of 3344 patients treated with pertuzumab.
[d] This denotes an adverse reaction reported in association with fatal outcome.
[e] The incidences of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA Preferred Terms reported in the individual studies.
[f] Observed with Phesgo only.
[g] Observed in the post-marketing setting.

Description of selected undesirable effects from clinical trials

Phesgo

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

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

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

Hypersensitivity reactions/anaphylaxis
In the FEDERICA trial, the overall frequency of hypersensitivity/anaphylaxis events reported in association with HER2-targeted therapy was 1.6% both in the Phesgo-treated patients and in the patients treated with intravenous pertuzumab and trastuzumab, and none of these events was NCI-CTCAE (version 4) grade 3-4 (see "*Warnings and precautions*").

Intravenous pertuzumab and trastuzumab

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

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

In the TRYPHAENA trial, the incidence of LVD (during the overall treatment period) was 8.3% in the group receiving pertuzumab plus trastuzumab and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by pertuzumab plus

trastuzumab and docetaxel; 9.3% in the group receiving pertuzumab plus trastuzumab and docetaxel after FEC; and 6.6% in the group treated with pertuzumab in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group receiving pertuzumab plus trastuzumab and docetaxel after FEC *(excluding a patient with symptomatic LVD during FEC treatment before receiving pertuzumab plus trastuzumab and docetaxel)* and also 1.3% in the group receiving pertuzumab in combination with TCH. No patients in the group treated with pertuzumab plus trastuzumab and FEC followed by pertuzumab plus trastuzumab and docetaxel experienced symptomatic LVD.

In the neoadjuvant phase 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 pertuzumab plus trastuzumab and paclitaxel, while none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by pertuzumab in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (ejection fraction decreased according to preferred term NCI-CTCAE v.4) was 7% in the group treated with dose-dense AC followed by pertuzumab plus trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by pertuzumab plus trastuzumab and docetaxel.

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

Infusion-related reaction
An infusion-related reaction 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 the CLEOPATRA trial, the initial dose of pertuzumab was given the day before trastuzumab and docetaxel to enable investigation of pertuzumab-associated reactions. On the first day, when only pertuzumab was administered, the overall frequency of infusion-related reactions was 9.8% in the placebo group and 13.2% in the pertuzumab-treated group, with most reactions being mild or moderate. The most common infusion-related reactions (≥1.0%) in the pertuzumab-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 pertuzumab-treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia and vomiting (see "*Warnings and precautions*").

In trials of treatments in the neoadjuvant and adjuvant settings, pertuzumab was administered on the same day as the other study medications. Infusion-related reactions occurred in 18.6%-25.0% of patients on the first day of pertuzumab administration (in combination with trastuzumab and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with most reactions being mild or moderate.

Hypersensitivity/anaphylaxis
In CLEOPATRA, the overall frequency of events reported as hypersensitivity/anaphylaxis was 9.3% in the patients of the placebo group and 11.3% in the pertuzumab-treated patients, with 2.5% and 2.0% of these events, respectively, being NCI-CTCAE (version 3) grade 3-4. Overall, 2 patients in the placebo group and 4 patients in the pertuzumab-treated group experienced anaphylaxis (see "*Warnings and precautions*").

Overall, most hypersensitivity reactions were mild or moderate and resolved during treatment. Based on changes to the study treatment, most reactions were classified as secondary to docetaxel infusions.

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

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

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

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

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

Switching from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa)
Switching from (or to) intravenous pertuzumab and trastuzumab did not raise any new or clinically relevant safety concerns. The observed adverse events were consistent with those reported in the FEDERICA study and in earlier studies with the intravenous dosage forms of pertuzumab and trastuzumab (see "*Clinical efficacy*").

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reaction via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code
L01XY02

Mechanism of action
Pertuzumab and trastuzumab are recombinant, humanised monoclonal antibodies of the immunoglobulin subtype IgG1κ targeting 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 different HER2 epitopes, namely subdomains II and IV, without competing and have complementary mechanisms for disrupting HER2 signalling. This results in enhanced antiproliferative activity *in vitro* and *in vivo* when pertuzumab and trastuzumab are used in combination.

In addition, the Fc part of the IgG1 framework of the two antibodies strongly activates antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, both pertuzumab and trastuzumab ADCC acts primarily on HER2-overexpressing cancer cells rather than cancer cells that do not overexpress HER2.

Pharmacodynamics
Clinical efficacy
This section describes clinical experience with the use of Phesgo and intravenous pertuzumab in combination with trastuzumab in patients with HER2-positive early and metastatic breast cancer. In all the studies below, HER2 overexpression was determined in a central laboratory and defined as 3+ IHC or ISH amplification ratio ≥2.0.

Early breast cancer

Phesgo fixed dose combination of pertuzumab and trastuzumab

FEDERICA WO40324
FEDERICA is an open-label, multicentre, randomised study in 500 patients with HER2-positive, resectable early breast cancer or with locally advanced (including inflammatory) breast cancer with tumour size >2 cm or node-positive breast cancer in the neoadjuvant and adjuvant setting*. Patients were randomised to receive 8 cycles of neoadjuvant chemotherapy with concurrent administration of 4 cycles of either Phesgo or intravenous pertuzumab and trastuzumab during cycles 5 to 8. Investigators selected one of the following two 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 in the first cycle and then 100 mg/m² in subsequent cycles at the investigator's discretion) every 3 weeks.

* The use of Phesgo in patients with metastatic breast cancer is based on extrapolation of data from intravenous administration.

Following surgery, patients continued therapy with Phesgo or intravenous pertuzumab and trastuzumab as treated prior to surgery for an additional 14 cycles, to complete 18 cycles of HER2-targeted therapy. Patients also received adjuvant radiotherapy and endocrine therapy as per local practice. In the adjuvant setting, the use of intravenous trastuzumab instead of subcutaneous trastuzumab was permitted at the investigator's discretion. HER2-targeted therapy was administered every 3 weeks as shown in Table 3 below:

Table 3: Dosing and administration of Phesgo, intravenous pertuzumab, intravenous trastuzumab and subcutaneous trastuzumab

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

FEDERICA was designed to demonstrate non-inferiority of the cycle 7 (i.e. pre-dose cycle 8) serum trough concentration (C_{trough}) of pertuzumab in Phesgo compared to intravenous pertuzumab (primary endpoint). Additional secondary endpoints included non-inferiority of the cycle 7 serum trough concentration (C_{trough}) of trastuzumab in Phesgo compared to intravenous trastuzumab, efficacy (total pathological complete response, tpCR) and safety outcomes. Demographics were balanced between the two treatment arms and the median age of patients treated in the study was 51 years. All except two patients were female. Most patients were node-positive (57.6%), had a hormone receptor-positive tumour (61.2%) and were Caucasian (65.8%).

Non-inferiority of exposure to pertuzumab and trastuzumab in Phesgo was demonstrated (see "*Pharmacokinetics*"). The analysis of secondary efficacy endpoint tpCR, defined as absence of invasive disease in the breast and axilla (ypT0/is, ypN0) is shown in Table 4.

Table 4: Summary of total pathological complete response (tpCR)

	Phesgo (n=248)	Intravenous pertuzumab + trastuzumab (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 (s.c. arm minus i.v. arm)	0.15	
95% CI for difference in tpCR rate[2]	-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.

PHranceSCa (MO40628)
Study MO40628 evaluated the safety of switching from intravenous pertuzumab and trastuzumab to Phesgo (and vice versa), with patient preference for Phesgo assessed as primary endpoint.
A total of 160 patients were enrolled in this two-arm crossover study: 80 patients were randomised to arm A (3 cycles of intravenous pertuzumab and trastuzumab, followed by 3 cycles of Phesgo) and 80 patient were randomised to arm B (3 cycles of Phesgo, followed by 3 cycles of intravenous pertuzumab and trastuzumab). The patients were subsequently able to choose whether to continue treatment with intravenous pertuzumab and trastuzumab or with Phesgo to complete 18 cycles of HER2-targeted therapy.

According to the primary analysis, 136 of 160 patients (85%) reported preferring subcutaneous Phesgo to intravenous pertuzumab and trastuzumab. The most common reason was that administration required less time in the clinic. 22 of 160 patients (14%) reported preferring intravenous pertuzumab and trastuzumab to Phesgo. The most common reason was that administration was perceived as more pleasant. Two of 160 patients (1%) preferred neither route of administration.

Among patients in arm A, the incidence of adverse events was similar after switching from intravenous pertuzumab and trastuzumab to Phesgo. In arm A, the incidence of adverse events was 77.5% during cycles 1 to 3 (i.v.) and 72.5% during cycles 4 to 6 (s.c.). In arm B, the incidence of adverse events was 77.5% during cycles 1 to 3 (s.c.) and 63.8% during cycles 4 to 6 (i.v.). The total number of events was higher during cycles 1 to 3 than during cycles 4 to 6, regardless of the therapy administered.

Intravenous pertuzumab and trastuzumab
Further information and clinical data on intravenous pertuzumab and trastuzumab can be found in the "Clinical efficacy" section of the Perjeta Information for healthcare professionals. This also includes a description of the design and results of pivotal studies conducted in patients with HER2-positive early or metastatic breast cancer.

Safety and efficacy in elderly patients
No overall differences in efficacy and safety of Phesgo were observed in patients ≥65 (n=26) and those <65 years of age (n=222).
However, with intravenous pertuzumab in combination with trastuzumab, the incidence of the following all-grade adverse events in patients ≥65 years of age (n=418) was at least 5% higher than in patients <65 years of age (n=2926): decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesaemia and diarrhoea.

Safety and efficacy in paediatric patients
The safety and efficacy of Phesgo in children and adolescents under 18 years of age have not been established.

Pharmacokinetics

Table 5 shows the exposure to pertuzumab and trastuzumab after subcutaneous administration of Phesgo (1200 mg pertuzumab/600 mg trastuzumab as a loading dose, followed by 600 mg pertuzumab/600 mg trastuzumab every 3 weeks) in the FEDERICA study. The pharmacokinetic (PK) results for the primary endpoint of pertuzumab cycle 7 (i.e. c 8) trough concentration (C_{trough}) showed the non-inferiority of pertuzumab in Phesgo (geometric mean 88.7 µg/ml) compared to intravenous pertuzumab (geometric mean 72.4 µg/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 in Phesgo and intravenous pertuzumab was 1.14, and thus greater than the predefined margin of 0.8.

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

Pooled PK data on pertuzumab in Phesgo and on intravenous pertuzumab from the FEDERICA trial provided the basis for creating a population PK model of pertuzumab with linear elimination from the central compartment in order to describe the PK concentrations of pertuzumab measured after subcutaneous administration of Phesgo and intravenous administration of pertuzumab.

Pooled data on trastuzumab PK from the BO22227 (HannaH) phase III study of subcutaneous trastuzumab *vs* intravenous trastuzumab provided the basis for creating a population PK model with parallel linear and non-linear elimination from the central compartment in order to describe the PK concentrations measured after intravenous or subcutaneous administration of trastuzumab in HER2-positive EBC patients. PK analysis using the population PK model from the HannaH study showed that pertuzumab in Phesgo had no effect on the PK of trastuzumab in Phesgo, since the PK of trastuzumab in Phesgo and the PK of subcutaneous trastuzumab were consistent.

Population PK-predicted pertuzumab and trastuzumab exposures are summarised in Table 5 below.

Table 5: Pertuzumab and trastuzumab exposure (median with 5th-95th percentiles) after subcutaneous administration of Phesgo or intravenous administration of pertuzumab or trastuzumab[a]

Parameter		Pertuzumab in Phesgo	Intravenous pertuzumab	Trastuzumab in Phesgo[b]	Intravenous trastuzumab[b]
C_{trough} (µg/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} (µg/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)
$AUC_{0\text{-}21\ days}$ (µg/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] Administration of the first dose of Phesgo, intravenous pertuzumab and trastuzumab in cycle 5.
[b] The population PK model from study BO22227 (HannaH) was used to simulate trastuzumab PK.

Absorption
The median maximum serum concentration (C_{max}) of pertuzumab in Phesgo and time to maximal concentration (T_{max}) were 157 µg/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 in Phesgo and time to maximal concentration (T_{max}) were 114 µg/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).

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

Based on population PK analysis, the volume of distribution of subcutaneously administered trastuzumab in the central (Vc) compartment in a typical patient was 2.91 l.

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

Elimination
Based on population pharmacokinetic (PK) analysis, the clearance of pertuzumab in 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 subcutaneously administered trastuzumab was 0.111 l/day. Trastuzumab concentrations are estimated to be <1 µg/ml (approximately 3% of the population-predicted $C_{min,ss}$, or about 97% washout) in at least 95% of patients 7 months after the last dose.

Kinetics in specific patient groups
Hepatic impairment
No formal pharmacokinetic study of Phesgo has been conducted in patients with hepatic impairment.

Renal impairment
No formal PK studies of Phesgo have been conducted in patients with renal impairment.

Population PK analysis of pertuzumab in Phesgo and of intravenous pertuzumab showed that renal impairment does not affect pertuzumab exposure, although the population PK analyses included only limited data from patients with severe renal impairment.

In a population pharmacokinetic analysis of subcutaneous and intravenous trastuzumab, renal impairment had no effect on trastuzumab disposition.

Elderly patients
No studies have been conducted to investigate the pharmacokinetics of Phesgo in elderly patients.

In population PK analyses of pertuzumab in Phesgo and of intravenous pertuzumab, age did not have a significant impact on pertuzumab PK.

In population PK analyses of subcutaneously and intravenously administered trastuzumab, age had no effect on trastuzumab disposition.

Children and adolescents
No studies have been conducted to investigate the pharmacokinetics of Phesgo in paediatric patients.

Preclinical data

No conventional safety pharmacology and toxicology studies have been conducted with Phesgo (combination of pertuzumab, trastuzumab and human hyaluronidase). However, studies are available on the individual agents and a bioavailability study has been conducted in the minipig.

Pertuzumab
Repeated-dose toxicity
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 diarrhoea was noted in association with treatment. In a subset of monkeys, chronic dosing (26 weekly doses) resulted in episodes of diarrhoea-induced dehydration that were managed with intravenous fluid replacement.

Mutagenicity/carcinogenicity
No studies have been performed to assess the mutagenic and carcinogenic potential of pertuzumab.

Reproductive toxicity
Reproductive toxicity studies were performed in cynomolgus monkeys with loading doses of 30 to 150 mg/kg and maintenance doses of 10 to 100 mg/kg, to achieve clinically relevant exposures. Intravenous administration of pertuzumab from gestation day (GD) 19 to 50 (period of organogenesis) was found to be embryotoxic and to result in a dose-dependent increase in embryo-fetal deaths between GD 25 and 70. Delayed renal development and oligohydramnios were identified (teratogenicity) on GD 100.

No specific fertility studies have been performed in animals to assess the effect of pertuzumab. No adverse effects on male or female reproductive organs were observed in repeated-dose toxicity studies of up to 6 months' duration in cynomolgus monkeys.

Trastuzumab
Repeated-dose toxicity
Trastuzumab was well tolerated in mice (non-binding species), rabbits (non-binding species) and macaques (rhesus and cynomolgus monkeys) (binding species) in single-dose (i.v.) and multiple-dose (s.c. and i.v.) toxicity studies lasting 13 weeks (25 mg/kg twice weekly or 26 weeks (25 mg/kg weekly). There was no evidence of acute or chronic toxicity.

Measurable systemic concentrations of the recombinant human enzyme hyaluronidase (rHuPH20) are unlikely as they were not detected in any patient in clinical trials of subcutaneous trastuzumab.

Mutagenicity/carcinogenicity
No mutagenicity data have been reported. No studies have been performed to evaluate the carcinogenic potential of trastuzumab.

Reproductive toxicity
Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg intravenous trastuzumab without producing evidence of harm to the fetus. Placental transfer of trastuzumab was observed during the early (gestation days 20-50) and late (gestation days 120-150) fetal development period.

In a study in cynomolgus monkeys given trastuzumab at doses 25 times the weekly human maintenance dose of 2 mg/kg intravenous trastuzumab on days 120 to 150 of gestation, trastuzumab was excreted in the milk post partum. Trastuzumab exposure *in utero* and the presence of trastuzumab in the serum of infant monkeys were not associated with adverse effects on their growth or development from birth to 1 month of age.

No animal studies have been performed to evaluate the effect of trastuzumab on fertility in male animals.

Other data (local toxicity)
Subcutaneous trastuzumab with human hyaluronidase was well tolerated in a local tolerance study in rabbits (non-binding species) and in a 13-week repeated-dose toxicity study in cynomolgus monkeys (binding species).

Phesgo (pertuzumab/trastuzumab)
Local toxicity
In a bioavailability study in the minipig, clinical observation revealed no findings after single subcutaneous doses of pertuzumab with rHuPH20 and pertuzumab in combination with trastuzumab and rHuPH20.

Other data (hyaluronidase)
Phesgo contains the recombinant human enzyme hyaluronidase (rHuPH20) as an excipient, which is used to improve the distribution and absorption of subcutaneously coadministered drugs. Measurable systemic concentrations of rHuPH20 are unlikely after local subcutaneous administration of Phesgo and were not observed in patients in Phesgo clinical trials.

In a 39-week toxicity study encompassing both general toxicity endpoints and specific fertility endpoints (cycle analysis, hormone measurements, sperm analysis and histological examination of reproductive organs) in sexually mature male and female monkeys, rHuPH20 was found to be well tolerated. Neither rHuPH20 nor anti-rHuPH20 antibodies that had been shown to neutralise endogenous cynomolgus hyaluronidase affected sperm, hormones, menstruation or the histological appearance of the reproductive organs.

In a further study, male and female monkeys were immunised with recombinant cynomolgus PH20 and produced significant immune responses. The antibodies recognised both the monkey PH20 and acrosomal hyaluronidase. Eight of 14 females in the group of PH20-immunised monkeys became pregnant, as did 6 of 14 in the control group. There was no association between fertility and antibody titres.

Studies in rabbits investigated the effects of neutralising antibodies to rHuPH20 and endogenous hyaluronidase on reproductive parameters and embryonic development. Detailed assessments of offspring until adulthood and of mating results identified no adverse effects on male or female fertility or on embryo-fetal development.

An embryonic/fetal development study with rHuPH20 in mice revealed no evidence of teratogenicity.

Studies of rHuPH20 in mice showed reductions in fetal weight and increased resorption rates. These effects occurred after rHuPH20 exposures that were markedly higher than that expected after subcutaneous administration of Phesgo in humans. Comparable human systemic exposure could occur if a bolus dose of Phesgo were inadvertently administered.

The comprehensive assessment of all available animal studies showed no effect of anti-rHuPH20 antibodies on male or female fertility or offspring development.

Other information

The solution containing 1200 mg pertuzumab/600 mg trastuzumab and the solution containing 600 mg pertuzumab/600 mg trastuzumab are ready-to-use solutions for injection and should not be mixed or diluted with other medicinal products.

Phesgo should be visually inspected for particulate matter or discolouration before use. Do not shake.

Phesgo solution for injection is for single use only and should be prepared by a qualified healthcare professional according to aseptic criteria.

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

Shelf life
Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening
For reasons of hygiene, the medicinal product should be used immediately after transferring it from the vial to the syringe, as it 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 for 24 hours at 9°C-30°C.

Once the solution has been transferred to the syringe, it is recommended that the transfer needle be replaced by a syringe closing cap to prevent the solution from drying in the needle and to avoid compromising the quality of the medicinal product. Label the syringe with the peel-off sticker. The injection needle must only be attached to the syringe immediately before administration to the patient. The volume should then be adjusted to 10 ml (600 mg pertuzumab/600 mg trastuzumab) or 15 ml (1200 mg pertuzumab/600 mg trastuzumab).

Disposal of unused/expired drugs
The release of medicinal products into the environment should be minimised. Medicinal products should not be disposed of via the wastewater system. Disposal in domestic waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medical 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 and/or waste material should be disposed of in accordance with local requirements.

Special precautions for storage
Store in the refrigerator (2-8°C).

Do not freeze.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

Authorisation number

67828 (Swissmedic).

Packs

1 vial containing 1200 mg pertuzumab/600 mg trastuzumab/15 ml [A]
1 vial containing 600 mg pertuzumab/600 mg trastuzumab/10 ml [A]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd, Basel.

Date of revision of the text

April 2021.

Made for
F. Hoffmann-La Roche Ltd, Basel, Switzerland
by F. Hoffmann-La Roche Ltd Switzerland,
Wurmisweg, Kaiseraugst, CH-4303