Pertuzumab/Trastuzumab (Phesgo®) and Vinorelbine[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Pertuzumab/trastuzumab (Phesgo®) and vinorelbine for the treatment of adult 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 where patients are deemed clinically unsuitable for taxane based therapy	C50	00798a	Pertuzumab/ Trastuzumab (Phesgo®): ODMS 20/12/2022 Vinorelbine – Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment is administered every 21 days in responding patients until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Cycle 1: Pertuzumab/ trastuzumab (Phesgo®) loading dose

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1	1	Pertuzumab/ trastuzumab (Phesgo®)	1200mg/ 600mg	SC (Observe for 30 minutes post injection [a])	Over 8 mins
2	1 and 8	vinorelbine[b]	[c]25mg/m^2	IV infusion	50ml 0.9% NaCl over 15min. Then flush the line with 250ml 0.9% sodium chloride prior to removing/capping IV access
[a]Patients should be observed for injection-related reactions and hypersensitivity reactions.Observation period should start following administration of Phesgo® and be completed prior to any subsequent administration of chemotherapy.Any deviation should be noted in local policies.					
[b]Vinorelbine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here.					
[c]Vinorelbine dose may be initiated or increased to 35 mg/m^2 at the treating physician's discretion.					

Cycle 2 and subsequent cycles

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pertuzumab/ trastuzumab (Phesgo®)	600mg/ 600mg	SC (Observe for 15 minutes post injection[a])	Over 5 mins if no adverse reactions	Every 21 days
2	1 and 8	Vinorelbine[b]	[c]30mg/m^2	IV infusion	50ml 0.9% NaCl over 15min. Then flush the line with 250ml 0.9% sodium chloride prior to removing/capping IV access	Day 1 and 8 of a 21 day cycle
[a]Patients should be observed for injection-related reactions and hypersensitivity reactions. Observation period should start following administration of Phesgo® and be completed prior to any subsequent administration of chemotherapy. Any deviation should be noted in local policies.						
[b]Vinorelbine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here.						
[c]Vinorelbine dose may be initiated or increased to 35 mg/m^2 at the treating physician's discretion.						

ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- ECOG status 0-1
- LVEF ≥ 50%
- Patients deemed clinically unsuitable for taxane based therapy

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, vinorelbine, or any of the excipients
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months)
- Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction with trastuzumab
- Pregnancy
- Lactation

USE with CAUTION:

- Neutrophil count < 1.5 x 10^9/L or severe infection; current or recent (within 2 weeks)
- Platelet count < 100 x 10^9/L

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)
- Assessment of peripheral neuropathy

Regular tests:

- FBC, renal and liver profile before each cycle
- MUGA scan or echocardiogram every 12 weeks during treatment with pertuzumab/trastuzumab (Phesgo®) and at completion of therapy. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

Pertuzumab/trastuzumab (Phesgo®):

- None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs. Please see Table 1 below for recommendations on resuming dosing pertuzumab and trastuzumab after a dose delay or missed doses.
- Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.

Table 1: Delayed or missed doses of pertuzumab and trastuzumab (Phesgo®)

Time between two sequential infusions	Dose modification
<6 weeks	The maintenance dose of pertuzumab/trastuzumab (Phesgo®) 600 mg/600 mg should be administered as soon as possible. Thereafter, continue with the 3-weekly schedule.
≥6 weeks	A loading dose of pertuzumab/trastuzumab (Phesgo®) 1200 mg/600 mg should be re-administered followed by maintenance dose of pertuzumab/trastuzumab (Phesgo®) 600 mg/600 mg every 3 weeks thereafter.

Table 2: Switching from intravenous pertuzumab and trastuzumab administration to Phesgo®

Time since last dose	Dose of Phesgo®
<6 weeks	Administer as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab and every 3 weeks for subsequent administrations.
≥6 weeks	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.

Haematological:

Table 3: Dose modification for Vinorelbine for haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1	and	≥100	100% Dose
0.5-0.99	or	75-99	Delay until recovery and reduce subsequent does to 80%

Renal and Hepatic Impairment:

Table 4: Dose modification in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment		
Pertuzumab/ trastuzumab (Phesgo®)	Dose adjustments 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 (PK) data available.	The safety and efficacy have not been studied in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment. No specific dose adjustment are recommended.		
Vinorelbine	No dose reduction required.	**AST/ALT**	**Bilirubin**	**Dose**
		>3 x ULN	> 2 x ULN	Reduce dose by 50%
		ULN= Upper Limit of Normal		

Management of adverse events:

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Pertuzumab and Trastuzumab (Phesgo®)	
LVEF < 40% or 40-45% associated with ≥10% points below the pre-treatment value.	Withhold treatment with pertuzumab/trastuzumab (Phesgo®). Repeat LVEF within 3 weeks. No improvement or further decline, consider discontinuation. Discuss with consultant and refer to cardiologist.
Symptomatic heart failure	Discontinue
NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue
Vinorelbine	
Grade ≥3	Withhold treatment until recovery to grade 1 then reduce the dose to 80% of the original dose. Discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pertuzumab/trastuzumab (Phesgo®): Minimal **(Refer to local policy)**
Vinorelbine: Minimal **(Refer to local policy)**

PREMEDICATIONS:

- **Trastuzumab/pertuzumab (Phesgo®):** Not usually required unless the patient has had a previous hypersensitivity. Paracetamol and antihistamine cover should be considered. Patient should be educated about the possibility of delayed infusion-related symptoms.

OTHER SUPPORTIVE CARE:

- Patients should be counseled on the risk of constipation associated with the use of vinca alkaloids. Dietary interventions or prophylactic laxatives may be required.
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Febrile neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

Vinorelbine

- **Extravasation:** Vinorelbine causes pain and tissue necrosis if extravasated **(Refer to local guidelines).**
- **Constipation:** Constipation with vinorelbine should at a grade 1-2 be managed with dietary interventions or laxatives.

Pertuzumab/trastuzumab (Phesgo®)

- **Left ventricular dysfunction (including congestive heart failure):** 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 compared to trastuzumab and chemotherapy. In the adjuvant setting, the majority of cases of symptomatic heart failure reported were in patients who received anthracycline-based chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines based on studies with intravenous pertuzumab in combination with trastuzumab and chemotherapy. Phesgo® has 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. In addition, pertuzumab in combination with trastuzumab and chemotherapy has not been studied in patients with decreases in LVEF < 50 % during prior trastuzumab adjuvant therapy. Assess LVEF prior to initiation of Phesgo® and at regular intervals during treatment (e.g. once during

neoadjuvant treatment and every 12 weeks in the adjuvant and metastatic setting) to ensure that LVEF is within normal limits. If the LVEF has declined 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. Cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Phesgo® with an anthracycline. Based on the pharmacological actions of HER2-targeted agents and anthracyclines, the risk of cardiac toxicity might be expected to be higher with concomitant use of Phesgo® and anthracyclines than with sequential use.

- **Injection-related reactions/infusion-related reactions (IRRs):** Phesgo® has been associated with injection-related reactions. 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. 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 pertuzumab in combination with intravenous trastuzumab and chemotherapy.
- **Hypersensitivity reactions/anaphylaxis:** Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have been observed with pertuzumab in combination with trastuzumab and chemotherapy. The majority of anaphylactic reactions occurred within the first 6-8 cycles of treatment when pertuzumab and trastuzumab were given in combination with chemotherapy. Medicinal products to treat such reactions, as well as emergency equipment, should be available for immediate use. Phesgo® must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome. Phesgo® is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab or to any of its excipients.
- **Diarrhoea:** Phesgo® may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (≥ 65 years) 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 Phesgo® should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with Phesgo® may be reinstated.
- **Pulmonary events:** Severe pulmonary events have been reported with the use of trastuzumab. These events have occasionally been fatal. These events may occur as part of an infusion-related reaction or with a delayed onset. 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®. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

DRUG INTERACTIONS:

- A possible interaction with warfarin has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.
- Risk of drug interactions causing increased concentrations of vinorelbine with CYP3A inhibitors.
- Risk of drug interactions causing decreased concentrations of vinorelbine with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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3. Andersson M, Lopez-vega J et al. Efficacy and safety of pertuzumab and trastuzumab administered in a single infusion bag, followed by vinorelbine: velvet cohort 2 final results. Oncologist *2017;* 22**:** 1160-1168.
4. Bergen, E, Berghoff, S et al 2014. Taxanes plus trastuzumab compared to oral vinorelbine plus trastuzumab in her2-overexpressing metastatic breast cancer. Breast care 2014*;* (9**):** 344-8.
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6. BC Cancer Agency Protocol Summary BRAVTRVIN Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN) and vinorelbine.
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Version	Date	Amendment	Approved By
1	20/12/2022		Prof Maccon Keane
2	10/08/2023	Updated emetogenic potential of pertuzumab/trastuzumab (Phesgo)	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.