Pertuzumab and Trastuzumab (Phesgo®) Maintenance Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Pertuzumab / trastuzumab (Phesgo®) for the maintenance treatment of adult patients with HER2- positive metastatic or locally recurrent unresectable breast cancer, where this is a continuation of treatment for patients who have completed the chemotherapy component of the treatment.	C50	00785	ODMS 20/12/2022

* This is for post 2012 indications only.

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.

Patients should have already been treated with pertuzumab and trastuzumab in combination with:

- **DOCEtaxel** (Refer to NCCP Regimen 00204 Pertuzumab, Trastuzumab and DOCEtaxel Therapy – 21 day cycle) **OR**
- **PACLitaxel** (Refer to NCCP Regimen 00507 Pertuzumab, Trastuzumab and Weekly PACLitaxel Therapy – 21 day cycle) **OR**
- **Vinorelbine** (Refer to NCCP Regimen 00526 Pertuzumab, Trastuzumab and Vinorelbine)

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 treatment (SACT) is administered.

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

Day	Drug	Dose	Route	Rate	Cycle
1	Pertuzumab/ Trastuzumab (Phesgo®)	1200mg/600mg	SC Observe for 30 minutes post injection [a]	Over 8 minutes	Cycle 1 only

[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.

Cycle 2 and subsequent cycles:

Day	Drug	Dose	Route	Rate	Cycle
1	Pertuzumab/ Trastuzumab (Phesgo®)	600mg/600mg	SC Observe for 15 minutes post injection [a]	Over 5 minutes if no adverse reactions	Every 21 days

[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.

ELIGIBILITY:

- Indication as above
- HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. Please see *Recommendations on Reporting on HER2 Status in Breast Cancer Patients* here.
- ECOG status 0-1
- Patients should have a pre-treatment LVEF of ≥ 50%
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, murine proteins 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 co-morbidities may be at increased risk of a fatal infusion reaction with trastuzumab
- Pregnancy or breast feeding

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)

Regular tests:

- FBC, renal and liver profile before each cycle
- Cardiac function (MUGA or ECHO) every 12 weeks. 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:

- Any dose modification should be discussed with a Consultant.
- None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs. Please see Table 1 below for recommendations on resuming dosing with pertuzumab/trastuzumab (Phesgo®) after a dose delay or missed doses.

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.

Renal and Hepatic Impairment:

Table 3: Dose modification of pertuzumab/trastuzumab[a] (Phesgo®) in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
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.
[a] Phesgo (renal and hepatic – SPC)	

Management of adverse events:

Table 4: Dose modification of pertuzumab/trastuzumab (Phesgo®) based on adverse events

Adverse reactions	Recommended dose modification
LVEF < 40% or 40-45% associated with ≥10% points below the pre-treatment value	Withhold treatment for at least 3 weeks. Treatment may be resumed if the LVEF has recovered to > 45 %, or to 40-45 % associated with a difference of < 10 % points below pre-treatment values No improvement or further decline discuss with consultant and consider referral to cardiologist.
Symptomatic heart failure	Discontinue
Grade 4* hypersensitivity reactions	Discontinue
*NCI-CTCAE Grading	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here:

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

Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here

PREMEDICATIONS:

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: No specific recommendations

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.
- **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:

Consult current drug interaction databases and relevant SmPC.

REFERENCES:

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3. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment JAMA 1999;282:2299-301
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5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
6. Pertuzumab / Trastuzumab (Phesgo®) Summary of Product Characteristics. Last updated: 02/03/2022. Accessed: Dec 2023. Available here: https://www.ema.europa.eu/en/documents/product-information/phesgo-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	20/12/2022		Prof Maccon Keane
2	10/08/2023	Updated emetogenic potential of pertuzumab/trastuzumab	Prof Maccon Keane
3	12/04/2024	Regimen reviewed. - Updated information regarding HER2 and LVEF in Eligibility section - Updated Baseline and Regular Tests section - Updated Table 4 as per SPC - Updated Drug Interactions section - NCCP Standardisation	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.