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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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 – N/A

* 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.

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 minutes
2	1 and 8	Vinorelbine[b]	[c]25mg/m^2	IV infusion	50mL 0.9% NaCl over 15 minutes. Then flush the line with 250mL 0.9% NaCl 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 Available on the NCCP website .					
[c]Vinorelbine dose may be initiated or increased to 35 mg/m^2 at the treating physician's discretion.					

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

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 minutes if no adverse reactions	Every 21 days
2	1 and 8	Vinorelbine[b]	[c]30mg/m^2	IV infusion	50mL 0.9% NaCl over 15 minutes. Then flush the line with 250mL 0.9% NaCl 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 Available on the NCCP website .						
[c]Vinorelbine dose may be initiated or increased to 35 mg/m^2 at the treating physician's discretion.						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Alternative treatment tables for Pertuzumab/Trastuzumab (Phesgo®) and Vinorelbine (oral Vinorelbine)

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 minutes
2	1 and 8	Vinorelbine[b]	60mg*/m^2 once weekly **(MAX 120mg)**	PO	N/A
[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]Swallow whole with water, without chewing, sucking or dissolving capsule. It is recommended to administer the capsule with some food					
* If well tolerated, consider increasing dose to 80mg/m^2 from cycle 2 or 3. If the patient chews or sucks the capsule by error, the liquid is an irritant. Proceed to mouth rinses with water or preferably a normal saline solution. In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the doctor in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.					
In the case of vomiting within a few hours after drug intake, do not re-administer.					
Vinorelbine is commonly available as 20mg, 30mg and 80mg capsules. 30mg/ m^2 IV is equivalent to 80mg/m^2 PO and 25mg/m^2 IV is equivalent to 60mg/ m^2 PO.					

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 minutes if no adverse reactions	Every 21 days
2	1 and 8	Vinorelbine[b]	60mg*/m^2 **(MAX 120mg)**	PO	N/A	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]Swallow whole with water, without chewing, sucking or dissolving capsule. It is recommended to administer the capsule with some food.						
*If well tolerated, consider increasing dose to 80mg/m^2 from cycle 2 or 3. If the patient chews or sucks the capsule by error, the liquid is an irritant. Proceed to mouth rinses with water or preferably a normal saline solution. In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the doctor in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.						
In the case of vomiting within a few hours after drug intake, do not re-administer.						
Vinorelbine is commonly available as 20mg, 30mg and 80mg capsules. 30mg/ m^2 IV is equivalent to 80mg/m^2 PO and 25mg/m^2 IV is equivalent to 60mg/ m^2 PO.						

Table 1: Dose of vinorelbine (PO) required for appropriate ranges of body surface area (BSA)

BSA (m^2)	60mg/m^2 Dose (mg)	80mg/m^2 Dose (mg)
0.95 to 1.04	60	80
1.05 to 1.14	70	90
1.15 to 1.24	70	100
1.25 to 1.34	80	100
1.35 to 1.44	80	110
1.45 to 1.54	90	120
1.55 to 1.64	100	130
1.65 to 1.74	100	140
1.75 to 1.84	110	140
1.85 to 1.94	110	150
≥1.95	120	160

ELIGIBILITY:

- Indications as above
- HER2 overexpression or HER 2 gene amplification as determined by an accurate and validated assay. Please see *Recommendations on Reporting on HER2 Status in Breast Cancer Patients*- Available on the NCCP website
- 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
- Disease significantly affecting absorption
- Previous significant surgical resection of stomach or small bowel

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
- Cardiac function (MUGA or echocardiogram) 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:

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 2: 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 3: 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 4: 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 5: Dose modification in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Pertuzumab/ trastuzumab (Phesgo®) [a]	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 [b]	No dose adjustment is needed Haemodialysis : no need for dose adjustment is expected	Mild and moderate: no dose adjustment is needed Severe: consider 66% of original dose
[a] Phesgo® (renal and hepatic – SPC) [b] Vinorelbine (renal and hepatic – Giraud et al (2023))		

Management of adverse events:

Table 6: 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, discuss with consultant and consider referral to cardiology.
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:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting- Available on NCCP website

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

For information : Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on NCCP website

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

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. NCCP SACT Breast Clinical Advisory Group Evidence Review July 2018.
2. Andersson M, Lidbrink E et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the hernata study. J Clin Oncol 2011*:* 29**,** 264-71.
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.
5. Perez, A. lópez-vega, J et al . Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with her2-positive locally advanced or metastatic breast cancer: velvet cohort 1 final results. Breast cancer re*s* 2016; 18**:**126.
6. BC Cancer Agency Protocol Summary BRAVTRVIN Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN) and vinorelbine.
7. Tan A, et al. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2021 Jan; 22(1):85-97.Depierre A, Freyer J et al. Oral vinorelbine: Feasibility and safety profile Annals of Oncology 2001;12: 1677-1681
8. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/

9. 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

10. Vinorelbine (Navelbine ®) Summary of Product Characteristics .Accessed April 2024.Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1226-010-001_18122013162040.pdf

11. Vinorelbine (Navelbine®) 20mg soft capsule. SmPC. Last updated 08/01/2024. Accessed July 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0329-011-001_08012024110935.pdf

12. Pertuzumab/Trastuzumab (Phesgo®) Summary of Product Characteristics.Accessed July 2024 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 (Phesgo)	Prof Maccon Keane
3	14/10/2024	Reviewed. Addition of alternative PO vinorelbine treatment tables. Updated baseline and regular tests section. Updated renal and hepatic dose modifications section. Adverse Effects and Drug Interactions sections updated in line with NCCP standardisation.	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.