Pertuzumab/Trastuzumab (Phesgo®) and Weekly PACLitaxel Therapy - 21 day cycle[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Pertuzumab/trastuzumab (Phesgo®) is indicated in combination with PACLitaxel in 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 intolerant of, have had significant toxicity to or are deemed clinically unsuitable for DOCEtaxel	C50	00797a	Pertuzumab/ Trastuzumab (Phesgo®): ODMS 20/12/2022 PACLitaxel – 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 with pertuzumab/trastuzumab (Phesgo®) is administered on day 1, and PACLitaxel is administered on day 1, 8, 15 of a 21 day cycle. PACLitaxel should be continued for up to 8 cycles, pertuzumab and trastuzumab should be continued 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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pertuzumab/ trastuzumab (Phesgo®)	1200mg/600mg	SC (Observe for 30 minutes post injection[a])	Over 8 minutes	Cycle 1 only
2	1, 8, 15	PACLitaxel	80mg/m^2	IV infusion	250mL 0.9% NaCl over 1 hour[b]	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.						
[b]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						

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

Cycle 2 and subsequent cycles

Admin. Order	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, 8, 15	PACLitaxel	80mg/m^2	IV infusion	250mL 0.9% NaCl over 1 hour[b]	Day 1, 8, 15 of a 21 day cycle up to maximum of 8 cycles

[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]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.

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

ELIGIBILITY:

- Indications 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
- LVEF ≥ 50%

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab, PACLitaxel, 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
- Significant hepatic dysfunction, contraindicating PACLitaxel
- Baseline neutrophil count < 1.5 x 10^9/L
- Pregnancy
- Lactation

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.
- Assessment of peripheral neuropathy status as clinically indicated

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 modifications for PACLitaxel for haematological toxicity

ANC (x10^9/L)		Platelets	Dose	Dose after neutropenic sepsis
≥ 1.5	and	> 90	80mg/m^2	65mg/m^2
*1-1.49	or	70-90	65mg/m^2	50mg/m^2
< 1	or	< 70	Delay and reduce next dose to 65mg/m^2 or add G-CSF	Delay
Patients who cannot tolerate treatment after 2 dose reductions should be discussed with treating clinician regarding continuation of treatment.				

*** If ANC 1 to less than 1.5 and patient fit and well can consider full dose of 80 mg/m^2 at discretion of prescribing Consultant**

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.			
PACLitaxel	Renal impairment: no need for dose adjustment is expected. Haemodialysis: no need for dose adjustment is expected.	**ALT**		**Total bilirubin**	**Dose of PACLitaxel**
		< 10 x ULN	and	≤ 1.25 x ULN	No dose reduction
		< 10 x ULN	and	1.26-2 x ULN	75% of original dose
		< 10 x ULN	and	2.01-5 x ULN	50% of original dose
		≥ 10 x ULN	and/or	> 5 x ULN	Contraindicated

Management of adverse events:

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Pertuzumab/Trastuzumab (Phesgo®)	
LVEF < 40% or 40-45% associated with ≥10% points below the pre-treatment value.	Withhold treatment with pertuzumab/trastuzumab (Phesgo®) for at least 3 weeks. Pertuzumab and trastuzumab 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 cardiology.
Symptomatic heart failure	Discontinue
NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue
PACLitaxel	
Grade 2 peripheral neuropathy	Decrease dose by 10mg/m^2
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m^2.
≥ Grade 3 reaction	Discontinue
Patients who cannot tolerate treatment after 2 dose reductions should be discussed with treating clinician regarding continuation of treatment.	

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)**
PACLitaxel: Low **(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) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

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.

PACLItaxel:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the premedication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**
- Table 6 outlines the suggested premedications prior to treatment with PACLitaxel.

Table 6: Suggested premedications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	dexAMETHasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	dexAMETHasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hour and 6 hour prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			

[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.

OTHER SUPPORTIVE CARE:

- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.
- G-CSF support may be required **(Refer to local policy)**

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. Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer. J Clin Oncol 2015;33:442-47.
2. Bachelot, T., E. Ciruelos, T. Peretz-Yablonski, et al. First-line pertuzumab (P), trastuzumab (H), and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC): Interim safety results (N=704) from PERUSE. ASCO Meeting Abstracts 2014;32(15_suppl):548.
3. Yu AF, Manrique C, Pun S, et al. Cardiac safety of paclitaxel plus trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer. The Oncologist 2016;21(4):418–24.
4. 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.
5. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment JAMA 1999;282:2299-301.
6. 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/
7. 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
8. NCCP Supportive Care Antiemetic Medicines for Inclusion in NCIS (Medical Oncology). V7 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/antiemetic-medicines-for-inclusion-in-ncis-medical-oncology-.pdf
9. Pertuzumab/Trastuzumab Summary of Product Characteristics. Last updated 02/03/2022. Accessed 14/03/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/phesgo-epar-product-information_en.pdf
10. PACLitaxel. Summary of Product Characteristics. Last updated 21/09/2022. Accessed 15/03/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-050-001_21092022103217.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	10/07/2024	Regimen reviewed. - Updated information regarding HER2 in Eligibility - Updated regular tests. - Updated PACLitaxel renal and hepatic dose modifications - Updated Table 5: Dose modification schedule based on adverse events - Updated PACLitaxel premedications - Adverse Effects and Drug Interactions sections removed and replaced with standard wording.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of Pertuzumab/Trastuzumab (Phesgo®) and PACLitaxel in Ireland. Patients should be informed of this 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 fully aware of their responsibility in communicating any relevant information to the patient and also 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.