Pertuzumab,Trastuzumab and Vinorelbine[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Pertuzumab in combination with trastuzumab 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	00526a	Pertuzumab -ODMS Trastuzumab –N/A 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 and trastuzumab loading doses

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1 or 2	1	Pertuzumab	840mg	IV Observe for 1hr post infusion	250mL 0.9% NaCl over 60 minutes
2 or 1	1	Trastuzumab	8mg/kg	IV infusion Observe post infusion [a]	250mL 0.9% NaCl over 90 minutes
3	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]Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. 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.

Cycles 2 and subsequent cycles

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion Observe for 30-60 minutes post infusion[a]	250mL NaCl 0.9% over 30 minutes if no adverse reactions.[b]	Every 21 days
2 or 1	1	Trastuzumab	6mg/kg	IV infusion Observe post infusion[c]	250mL NaCl 0.9% over 30 minutes [d]	Every 21 days
3	1 and 8	Vinorelbine[e]	[f]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]Observation period not required after 3 consecutive treatments with pertuzumab with no reaction.

[b]The infusion time of 30-60 minutes may be used at the discretion of the prescribing consultant.

[c]Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.

[d]Trastuzumab is incompatible with glucose solution.

[e] 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

[f] 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 - Pertuzumab,Trastuzumab and Vinorelbine (oral Vinorelbine)

Cycle 1: Pertuzumab and trastuzumab loading dose

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1 or 2	1	Pertuzumab	840mg	IV Observe for 1hr post infusion	250mL 0.9% NaCl over 60 minutes
2 or 1	1	Trastuzumab	8mg/kg	IV infusion Observe post infusion [a]	250mL 0.9% NaCl over 90 minutes
3	1 and 8	Vinorelbine[b]	60mg*/m^2 once weekly **(MAX 120mg)**	PO	N/A

[a]Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.

*If well tolerated, consider increasing dose to 80mg/m^2 from cycle 2 or 3.
[b]Swallow whole with water, without chewing, sucking or dissolving capsule. It is recommended to administer the capsule with some food
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.

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

Cycles 2 and subsequent cycles

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion Observe for 30-60 minutes post infusion[a]	250mL NaCl 0.9% over 30 minutes if no adverse reactions.[b]	Every 21 days
2 or 1	1	Trastuzumab	6mg/kg	IV infusion Observe post infusion[c]	250mL NaCl 0.9% over 30 minutes [d]	Every 21 days
3	1 and 8	Vinorelbine[e]	60mg*/m^2 **(MAX 120mg)**	PO	N/A	Day 1 and 8 of a 21 day cycle
[a]Observation period not required after 3 consecutive treatments with pertuzumab with no reaction.						
[b]The infusion time of 30-60 minutes may be used at the discretion of the prescribing consultant.						
[c]Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.						
[d]Trastuzumab is incompatible with glucose solution.						
[e]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 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.						

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

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:

- Any dose modification should be discussed with a Consultant
- **Pertuzumab and trastuzumab**
  - None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs.
  - Discontinue pertuzumab if trastuzumab is discontinued.
  - If vinorelbine is discontinued due to toxicity, antibody therapy can be continued until disease progression; if antibody therapy is discontinued due to toxicity, vinorelbine can be continued until disease progression
- **Delayed or missed doses**
  - If the time between two sequential infusions is < 6 weeks, the 420 mg dose of pertuzumab should be administered as soon as possible without regard to the next planned dose.
  - Re-load pertuzumab if the time between two sequential infusions is ≥ 6 weeks or more.
  - Re-load trastuzumab if the time between two sequential infusions is ≥ 6 weeks.
  - If re-loading is required for either drug, the 3 drugs should be given in the same schedule as Cycle 1.
  - The next cycle should follow 21 days from the re-loading dose.

Haematological:

Table 2: 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 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
Pertuzumab	No dose adjustment is needed. Haemodialysis: no need of dose adjustment is expected.		No need of dose adjustment is expected.
Trastuzumab	**CrCl mL/minute**	**Dose reduction**	No need for dose adjustment is expected.
	≥ 30	No dose adjustment is needed	
	< 30	No need for dose adjustment is expected	
	Haemodialysis	No need for dose adjustment is expected	
Vinorelbine	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

Management of adverse events:

Table 4: Dose modification schedule 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 with pertuzumab and trastuzumab 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
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
*NCI-CTCAE Grading	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

  - **Pertuzumab** Minimal (**Refer to local policy).**
  - **Trasuzumab** 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 and pertuzumab: 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:

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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.
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6. BC Cancer Agency Protocol Summary BRAVTRVIN Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN) and vinorelbine- http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Breast/BRAVTRVIN_Protocol.pdf revised August 2016
7. 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
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11. Pertuzumab *(*PERJETA®) Summary of Product Characteristics. Accessed July 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/perjeta-epar-product-information_en.pdf
12. Vinorelbine (Navelbine®) Summary of Product Characteristics. Accessed July 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1226-010-001_18122013162040.pdf
13. 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

Version	Date	Amendment	Approved By
1	07/11/2018		Prof Maccon Keane
2	2/5/2019	Updated trastuzumab and pertuzumab infusion time from cycle 2 onwards. Update emetogenic potential.	Prof Maccon Keane
3	10/11/2020	Reviewed	Prof Maccon Keane
4	10/08/2023	Updated emetogenic potential of pertuzumab	Prof Maccon Keane

5	14/10/2024	Addition of alternate treatment table for PO vinorelbine. Update to eligibility section and regular tests section. Update to Table 3 to align with Giraud et al (2023). Update to Table 4 with amended standard wording. 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.