Pertuzumab Trastuzumab and Vinorelbine

**INDICATIONS FOR USE:**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>C50</td>
<td>00526a</td>
<td>Pertuzumab-ODMS Trastuzumab-Hospital Vinorelbine – Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

**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 patient's 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 trastuzumab and pertuzumab are administered.

**Cycle 1: Pertuzumab and trastuzumab loading doses**

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2</td>
<td>1</td>
<td>Pertuzumab</td>
<td>840mg</td>
<td>IV Observe for 1 hr post infusion</td>
<td>250ml 0.9% NaCl over 60min</td>
</tr>
<tr>
<td>2 or 1</td>
<td>1</td>
<td>Trastuzumab</td>
<td>8mg/kg</td>
<td>IV infusion Observe post infusion a</td>
<td>250ml 0.9% NaCl over 90min</td>
</tr>
<tr>
<td>3</td>
<td>1 and 8</td>
<td>Vinorelbine b</td>
<td>25mg/m²</td>
<td>IV infusion</td>
<td>50ml 0.9% NaCl over 15min. Then flush the line with 250ml 0.9% sodium chloride prior to removing/capping IV access</td>
</tr>
</tbody>
</table>

aRecommended 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.

bVinorelbine 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.

cVinorelbine dose may be initiated or increased to 35 mg/m² at the treating physician's discretion.
Cycles 2 and subsequent cycles

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2</td>
<td>1</td>
<td>Pertuzumab</td>
<td>420mg</td>
<td>IV infusion</td>
<td>250ml NaCl 0.9% over 30min if no adverse reactions.a</td>
<td>Every 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observe for 30-60mins post infusiona</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or 1</td>
<td>1</td>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>IV infusion</td>
<td>250ml NaCl 0.9% over 30 min d</td>
<td>Every 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observe post infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Vinorelbine</td>
<td>30mg/m²</td>
<td>IV infusion</td>
<td>50ml 0.9% NaCl over 15min. Then flush the line with 250ml 0.9% sodium chloride prior to removing/capping IV access</td>
<td>Day 1 and 8 of a 21 day cycle</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aObservation period not required after 3 consecutive treatments with pertuzumab with no reaction.

bThe infusion time of 30-60 minutes may be used at the discretion of the prescribing consultant

cRecommended 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.

dTrastuzumab is incompatible with glucose solution

eVinorelbine 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

fVinorelbine dose may be initiated or increased to 35 mg/m² at the treating physician’s discretion.

ELIGIBILITY:
- Indications as above
- HER2 positive as demonstrated by a validated test method
- Life expectancy > 3 months
- 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 10⁹/L or severe infection; current or recent (within 2 weeks)
- Platelet count < 100 x 10⁹/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 trastuzumab 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:
- 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 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 1: Dose modification for vinorelbine for haematological toxicity

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>*Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>and ≥100</td>
<td>100% Dose</td>
</tr>
<tr>
<td>0.5-0.99</td>
<td>or 75-99</td>
<td>Delay until recovery and reduce subsequent does to 80%</td>
</tr>
</tbody>
</table>
Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab</td>
<td>No dose reduction required for mild or moderate renal impairment. No dose recommendations for severe impairment due to limited data.</td>
<td>No specific dose recommendations. Has not been studied in patients with hepatic impairment.</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>No dose reduction required.</td>
<td>No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>No dose reduction required.</td>
<td>AST/ALT Bilirubin Dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 x ULN &gt; 2 x ULN Reduce dose by 50% *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ULN= Upper Limit of Normal</td>
</tr>
</tbody>
</table>

Management of adverse events:

Table 3: Dose modification schedule based on adverse events

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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- Pertuzumab Low (Refer to local policy).
- Trastuzumab Minimal (Refer to local policy).
- Vinorelbine Minimal (Refer to local policy).

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 / 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.
- **Hypersensitivity/Infusion reactions**: There is a risk of hypersensitivity/infusion reactions with pertuzumab. Although hypersensitivity with trastuzumab is common, severe hypersensitivity reactions are uncommon. Use with caution in patients with dyspnoea at rest from pulmonary/cardiac conditions as increased risk of infusion related symptoms.
- **Cardiac toxicity**: Decreases in LVEF have been reported with medicinal products that block HER2 activity, including pertuzumab. Trastuzumab can produce declines in ventricular dysfunction and congestive heart failure (CHF). Baseline and 3 monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure. Special care should be taken when prescribing vinorelbine for patients with history of ischemic heart disease.
- **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

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.

ATC CODE:
- Pertuzumab - L01XC13
- Trastuzumab - L01XC03
- Vinorelbine - L01BC05

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


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>07/11/2018</td>
<td>Updated trastuzumab and pertuzumab infusion time from cycle 2 onwards. Update emetogenic potential.</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>2/5/2019</td>
<td>Updated trastuzumab and pertuzumab infusion time from cycle 2 onwards. Update emetogenic potential.</td>
<td>Prof Maccon Keane</td>
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</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
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.

ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/proinfo/medonc/cdmp/