Pertuzumab and Trastuzumab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Pertuzumab in combination with trastuzumab 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	00726a	Pertuzumab: ODMS Feb 2014 Trastuzumab: Hospital

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 pertuzumab and trastuzumab are administered.

Cycle 1 onwards:

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion Observe for 30-60mins post infusion[a]	250ml 0.9% sodium chloride over 30min if no adverse reactions[b]	Every 21 days
2 or 1	1	Trastuzumab[c]	6mg/kg	IV infusion[d] Observe post infusion[e]	250ml 0.9% sodium chloride over 30 min	Every 21 days
[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]Trastuzumab is incompatible with glucose solution.						
[d]Trastuzumab can be substituted with the subcutaneous formulation where this has been approved locally.						
[e]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.						

ELIGIBILITY:

- Indication as above
- HER2 positive as demonstrated by a validated test method
- ECOG status 0-1
- Patients should have a pre-treatment LVEF of ≥ 55%
- 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:

- HER2 positive as demonstrated by a validated test method
- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)

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.
- None usually recommended. Doses are held or discontinued if unacceptable toxicity occurs. Please see Table 1 below for recommendations on resuming dosing with pertuzumab and trastuzumab after a dose delay or missed doses.
- If trastuzumab treatment is discontinued, treatment with pertuzumab should be discontinued.

Table 1: Dose modifications of pertuzumab and trastuzumab for delayed or missed doses

Time between two sequential infusions	Pertuzumab	Trastuzumab
<6 weeks	The 420mg dose of pertuzumab should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.	The 6mg/kg dose of trastuzumab IV should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.
≥6 weeks	The 840mg loading dose of pertuzumab should be re-administered as a 60 min infusion, followed by a maintenance dose of 420mg IV administered every 3 weeks thereafter.	The loading dose of 8mg/kg of trastuzumab IV should be re-administered over approximately 90 min, followed by a maintenance dose of 6mg/kg IV administered every 3 weeks thereafter.

Renal and Hepatic Impairment:

Table 2: Dose modification of pertuzumab and trastuzumab in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Pertuzumab	No dose reduction required for mild or moderate renal impairment. No dose recommendations for severe impairment due to limited data.	No specific dose recommendations. Has not been studied in patients with hepatic impairment.
Trastuzumab	No dose reduction required.	No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.

Management of adverse events:

Table 3: Dose modification of pertuzumab and trastuzumab based on adverse events

Adverse reactions	Recommended dose modification
Reduction in LVEF to <50% -associated with a fall of ≥ 10% points below pre-treatment values.	Withhold treatment with pertuzumab and trastuzumab for at least 3 weeks. Pertuzumab and trastuzumab may be resumed if the LVEF has recovered to ≥50% or to a difference of <10% points below pre-treatment values. No improvement or further decline, consider discontinuation. Discuss with consultant and refer to cardiologist.
Symptomatic heart failure	Discontinue
Grade 4* hypersensitivity reactions	Discontinue
*NCI-CTCAE Grading	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pertuzumab: Minimal **(Refer to local policy)**
Trastuzumab: Minimal **(Refer to local policy)**

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.

Pertuzumab

- **Ventricular dysfunction (including congestive heart failure):** The incidence of symptomatic left ventricular systolic dysfunction (LVD) was higher in patients treated with pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy.
  Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who received anthracycline-based chemotherapy.
  Pertuzumab has not been studied in patients with: a pre-treatment LVEF value of < 50%; a prior history of congestive heart failure (CHF); LVEF declines to < 50% during prior trastuzumab adjuvant therapy; or 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 >360mg/m^2 of DOXOrubicin or its equivalent.
  Assess LVEF prior to initiation of pertuzumab and at regular intervals during treatment with pertuzumab (e.g. every 12 weeks in the adjuvant 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 pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.
- **Infusion reactions, hypersensitivity reactions/anaphylaxis:** Pertuzumab has been associated with infusion and hypersensitivity reactions. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions of Pertuzumab is recommended. If a significant infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.
  Pertuzumab must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome.
- **Diarrhoea:** Pertuzumab may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (≥ 65 years) may have a higher risk of diarrhoea compared with younger patients (< 65 years). 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 pertuzumab should be considered if no improvement in the patient's

condition is achieved. When the diarrhoea is under control treatment with pertuzumab may be reinstated.

Trastuzumab

- **Cardiac toxicity**:
  - Trastuzumab has been associated with moderate to severe cardiac failure. Baseline and three monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure.
  - If LVEF drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50 %, treatment should be withheld and a repeat LVEF assessment carried out within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.
  - Trastuzumab and anthracyclines should not be given concurrently in combination due to cardiotoxicity risk.
  - Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.
- **Trastuzumab infusion-associated symptoms:** Usually chills and fever may occur. Stop infusion and consider antihistamine cover. When symptoms have resolved the infusion may be recommenced. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.
- **Pulmonary events:** Severe pulmonary adverse reactions can occur in association with the use of trastuzumab and have been associated with a fatal outcome. These events may occur as part of an infusion-related reaction or with a delayed onset. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

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.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	13/04/2022		Prof Maccon Keane
2	22/06/2023	Updated emetogenic potential of pertuzumab	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.