Pertuzumab and Trastuzumab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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: 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.

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 systemic anti-cancer treatment (SACT) is administered.

Cycle 1 onwards:

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 or 2	1	Pertuzumab	420mg	IV infusion Observe for 30-60 minutes post infusion[a]	250mL 0.9% NaCl over 30 minutes if no adverse reactions[b]	Every 21 days
2 or 1	1	Trastuzumab[c]	6mg/kg	IV infusion Observe post infusion[d]	250mL 0.9% NaCl over 30 minutes	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]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.

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

ELIGIBILITY:

- Indication 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* here.
- ECOG status 0-1
- Patients should have a pre-treatment LVEF of ≥ 50%
- 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 breastfeeding

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.

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

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th>Hepatic Impairment</th></tr>
<tr><td>Pertuzumab [a]</td><td colspan="2">No dose adjustment is needed.

Haemodialysis: no need of dose adjustment is expected.</td><td>No need of dose adjustment is expected.</td></tr>
<tr><td rowspan="4">Trastuzumab [b]</td><td>CrCl (mL/minute):</td><td>Dose modification:</td><td rowspan="4">No need for dose adjustment is expected.</td></tr>
<tr><td>≥ 30</td><td>No dose adjustment is needed</td></tr>
<tr><td>< 30</td><td>No need for dose adjustment is expected</td></tr>
<tr><td>Haemodialysis</td><td>No need for dose adjustment is expected</td></tr>
<tr><td colspan="4">[a] Pertuzumab (renal and hepatic – Giraud et al 2023);
[b] Trastuzumab (renal and hepatic – Giraud et al 2023)</td></tr>
</table>

Management of adverse events:

Table 3: Dose modification of pertuzumab and trastuzumab 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 cardiologist.
Symptomatic heart failure	Discontinue
Grade 4* hypersensitivity reactions	Discontinue
*NCI-CTCAE Grading	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here:

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

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

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here

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 or metastatic 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 3 monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure.
  - 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:

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

REFERENCES:

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2. Baselga J et al. CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012 Jan 12; 366(2):109-19. doi: 10.1056/NEJMoa1113216. Epub 2011 Dec 7. PMID: 22149875; PMCID: PMC5705202.
3. 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
4. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment JAMA 1999;282:2299-301
5. Pertuzumab (Perjeta®) SmPC EMA. Last updated: 09/12/2021. Accessed Dec 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/perjeta-epar-product-information_en.pdf
6. Trastuzumab (Herceptin®) SmPC EMA. Last updated: 17/03/2023. Accessed Dec 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	13/04/2022		Prof Maccon Keane
2	22/06/2023	Updated emetogenic potential of pertuzumab.	Prof Maccon Keane
3	02/05/2024	Regimen reviewed. – Updated Treatment Table – Updated information regarding HER2 and LVEF in Eligibility section – Updated Baseline and Regular Tests section – Aligned Table 2 Pertuzumab and Trastuzumab renal and hepatic dose modifications to Giraud et al (2023)	Prof Maccon Keane

		– Updated information regarding LVEF in Table 3 as per SPC – Updated Adverse Effects section – Updated Drug Interaction section	
3a	29/05/2024	NCCP Standardisation	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.