

Pertuzumab and Trastuzumab and Chemotherapy Therapy - 21 day cycle

Please refer to the appropriate regimen for details of the chemotherapy regimen being administered in combination with pertuzumab and trastuzumab. ([NCCP Breast regimens](#))

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence	C50	00350a	Pertuzumab- ODMS 01/07/2020 Trastuzumab- Hospital Chemotherapy- Hospital
Pertuzumab in combination with trastuzumab and chemotherapy for the adjuvant treatment of adult patients with HER2-positive breast cancer at high risk of recurrence	C50	00350b	Pertuzumab- Reimbursement not approved ⁱ Trastuzumab- Hospital Chemotherapy- 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 patient's individual clinical circumstances.

NOTE

- In patients receiving an anthracycline-based regimen, pertuzumab and trastuzumab should only be administered following completion of the entire anthracycline regimen
- In patients receiving a taxane-based regimen pertuzumab and trastuzumab should start on Day 1 of the first taxane-containing cycle

Neoadjuvant treatment:

Pertuzumab is administered once every 21 days for 3 to 6 cycles in combination with neoadjuvant trastuzumab and chemotherapy, as part of a treatment regimen for early breast cancer. Following surgery, patients should be treated with adjuvant trastuzumab to complete 1 year of treatment. (Refer to [NCCP Breast regimens](#))

Adjuvant treatment:

Pertuzumab is administered once every 21 days in combination with trastuzumab and chemotherapy for a total of one year (up to 18 cycles or until disease progression, or unacceptable toxicity, whichever occurs first) as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include standard anthracycline and/or taxane-based chemotherapy. (Refer to [NCCP Breast regimens](#))

Facilities to treat anaphylaxis MUST be present when pertuzumab and trastuzumab are administered.

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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 60min
2 or 1	1	Trastuzumab ^a	8mg/kg	IV infusion Observe post infusion ^b	250ml 0.9% NaCl over 90min

^aTrastuzumab is incompatible with glucose solution

^bRecommended 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.

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 30-60mins post infusion ^a	250ml 0.9% NaCl over 30 min if no adverse reactions ^b	Every 21 days
2 or 1	1	Trastuzumab ^d	6mg/kg	IV infusion Observe post infusion ^c	250ml 0.9% NaCl over 30min	Every 21 days

^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

ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- ECOG status 0-1
- Patients should have a pre-treatment LVEF of $\geq 55\%$ ($\geq 50\%$ after completion of the anthracycline component of chemotherapy, if given)

EXCLUSIONS:

- Hypersensitivity to pertuzumab, trastuzumab 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 or breast feeding

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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.
- Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.
- If trastuzumab treatment is discontinued, treatment with pertuzumab should be discontinued.
- Pertuzumab and trastuzumab should continue even if the taxane-based chemotherapy is discontinued.
- For dose modifications of chemotherapy, please refer to the relevant [NCCP Breast Regimen](#).

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 60min 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 90min, followed by a maintenance dose of 6mg/kg IV administered every 3 weeks thereafter.

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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 $\geq 10\%$ points below pre-treatment values.	Withhold treatment with pertuzumab and trastuzumab for at least 3weeks. Pertuzumab and trastuzumab may be resumed if the LVEF has recovered to $\geq 50\%$ 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: Low (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

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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

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/m² 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 3 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.

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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.
- The half-life of trastuzumab is approximately 4-5 weeks
- **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 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.(3) 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.

ATC CODE:

Pertuzumab - L01XC13
 Trastuzumab - L01XC03

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5. Pertuzumab (Perjeta®) SmPC EMA. Last updated: 15/04/2019. Accessed July 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/perjeta-epar-product-information_en.pdf

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Version	Date	Amendment	Approved By
1	24/07/2019		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱ Post 2012 indication. Not reimbursed through the ODMS or Community Drug Schemes (including the High Tech arrangements of the PCRS community drug schemes). Please check <https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/new.html> for the most up to date reimbursement approvals.

ODMS – Oncology Drug Management System

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

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