Trastuzumab Subcutaneous 21 days - Early Breast Cancer

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Indicator
HER2 positive early breast cancer (EBC) Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)	C50	00285a	Hospital
Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with PACLitaxel or DOCEtaxel.		00285b	Hospital
In combination with adjuvant chemotherapy consisting of DOCEtaxel and CARBOplatin.		00285c	Hospital
In combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours >2cm in diameter		00285d	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.

Treatment administered once every 21 days for 1 year or until disease recurrence, whichever occurs first or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when trastuzumab is administered

Drug	Dose	Route	Cycle
Trastuzumab	600mg	SC over 2-5mins	Every 21 days
The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with trastuzumab subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.			
Patients should be observed for at least six hours after the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions. Any deviation should be noted in local policies.			

ELIGIBILTY:

- Indications as above
- HER-2 positive tumour as demonstrated by a validated test method.
- Life expectancy >3months
- ECOG 0-3
- In EBC, LVEF >55%* for trastuzumab therapy.
  * Many clinical trials have been conducted with LVEF ≥ 50%.(1) Clinical judgment should be exercised where patients fall between these two ranges.

EXCLUSIONS:

- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months). Hypersensitivity to trastuzumab or any of the excipients.
- Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- Blood renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- Blood renal and liver profile every 6 weeks
- Cardiac function 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. Discontinue if unacceptable toxicity occurs.
- If the patient misses a dose of sub-cutaneous trastuzumab it is recommended to administer the next 600mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive trastuzumab subcutaneous formulation administrations should not be less than three weeks.

Renal and Hepatic Impairment:

Table 1. Recommended dose modification for trastuzumab in patients with renal or hepatic impairment

Renal impairment	Hepatic impairment
No dedicated studies of trastazumab in patients with renal impairment have been conducted. Based on a population pharmacokinetic (PK) analysis renal impairment was not shown to affect trastuzumab disposition	No dedicated studies of trastazumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary

Management of adverse events:

Table 2: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
LVEF drops 10 ejection fraction points from baseline and to below 50%	Withhold treatment. Repeat LVEF after 3 weeks. No improvement or further decline consider discontinuation. Discuss with consultant and refer to cardiologist.
Symptomatic heart failure	Discontinue
Grade 4* hypersensitivity reactions	Discontinue
Haematological	Treatment may continue during periods of reversible, chemotherapy-induced myelosuppression. Monitor carefully for any complications of neutropenia.

*NCI-CTCAE Grading

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal **(Refer to local policy)**.

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity. Paracetamol and antihistamine cover should be considered.

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.

- **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. 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
- **Administration-related reactions (ARRs)**: Cases of ARRs have been reported with trastuzumab subcutaneous formulation. Patients should be observed for ARRs for six hours after the first injection and for two hours after subsequent injections. They can be treated with an analgesic/antipyretic such as paracetamol, or an antihistamine such as diphenhydramine. Pre-medication may be used to reduce risk of occurrence of ARRs.
- **Pulmonary events:** Caution is recommended with trastuzumab subcutaneous formulation as severe pulmonary events have been reported with the use of the intravenous formulation in the post-marketing setting. These events have occasionally been fatal and may occur as part of an infusion-related reaction or with 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.(2)
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Trastuzumab - L01XC03

REFERENCES:

1. Baselga J, Perez EA et al. Adjuvant Trastuzumab: A Milestone in the Treatment of HER-2-Positive Early Breast Cancer. The Oncologist 2006;11(suppl1):4–12
2. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment JAMA 1999;282:2299-301

3. Ismael G, Hegg R, Muehlbauer S et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I—III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. The Lancet Oncology. 2012;13:869–78.
4. Trastuzumab (Herceptin ®) Summary of Product Characteristics EMA. Last updated: 27/05/2019. Accessed August 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	15/9/2015		Prof Maccon Keane
2	20/09/2017	Clarification of dosing in renal and hepatic impairment. Updated emetogenic potential. Formatting in new NCCP Regimen Template	Prof Maccon Keane
3	21/08/2019	Updated adverse events	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.