Trastuzumab (IV) Monotherapy - 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
HER2 positive metastatic breast cancer (MBC)	C50	00200a	Hospital
HER2 positive early breast cancer (EBC)	C50	00200b	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.

MBC: Treatment administered every 21 days unless unacceptable toxicity develops.
EBC: Treatment administered every 21 days for 1 year or unless disease recurrence, or unacceptable toxicity.
Facilities to treat anaphylaxis MUST be present when trastuzumab is administered.

Cycle 1 For **NEW** patients **ONLY.**

Omit for patients continuing single-agent trastuzumab following a trastuzumab containing regimen.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	Trastuzumab	8mg/kg	IV infusion Observe post infusion[a]	250ml 0.9% sodium chloride[b] over 90min	1

Cycle 2 and subsequent cycles or for patients who have just completed a trastuzumab containing chemotherapy regimen:

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	Trastuzumab	6mg/kg	IV infusion Observe post infusion[a]	If no adverse reactions use 250ml 0.9% sodium chloride[b] over 30min	2 and further cycles

[a]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.

[b]Trastuzumab is incompatible with glucose solution.

[c]Trastuzumab can be substituted with the subcutaneous formulation where this has been approved locally.
Trastuzumab is administered subcutaneously at a dose of 600mg over 2-5minutes.
The injection site should be alternated between the left and right thigh.
New injections should be given at least 2.5 cm 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.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- 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). In EBC, LVEF > 55% for trastuzumab therapy.
- Hypersensitivity to trastuzumab, murine proteins 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:

- FBC
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- FBC every 6 weeks
- Cardiac function, LFTs, creatinine 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 trastuzumab by one week or less, then the usual maintenance dose of 6 mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.
- If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab (8 mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (6 mg/kg) should then be given every 3 weeks from that point.

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 trastuzumab 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 trastuzumab 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	Consider discontinuation – refer to cardiology for review. Clinical decision.
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.
- 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.

- **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.
  - 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. (2)
- Current drug interaction databases should be consulted for more information.

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. Slamon D, Leyland-Jones B, Shak S, Paton V et al. Addition of Herceptin™ (humanized anti-HER2 antibody) to first line chemotherapy for HER2 overexpressing metastatic breast cancer (HER2 +/MBC) markedly increases anticancer activity: a randomized, multinational controlled phase III trial. Proc Am Soc Clin Oncol 1998;17:98a.

4. Lee, R., D. Incekot, P. Ng.. Rapid 30 minute infusion of trastuzumab 6mg/kg every 3 weeks: cost effective and safe. J Oncol Pharmacy Practice 2006 ; 12(1):22
5. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. J Clin Oncol 2004;22:322-329
6. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. for the HERA trial study team (2005) Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. N Engl J Med 2005;353:1659-72
7. Perez, E. A., V. J. Suman, N. E. Davidson, et al.Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008; 26:1231-1238.
8. Russell, S. D., K. L. Blackwell, J. Lawrence, et al, Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 2010; 28:3416-3421.
9. Trastuzumab (Herceptin®) Summary of Product Characteristics EMA. Last updated 27/08/2020. Accessed April 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf
10. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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

Version	Date	Amendment	Approved By
1	10/2/2014		Prof Macon Keane
2	30/06/2015	Clarification of LVEF requirement in EBC	Prof Macon Keane
3	30/5/2017	Clarification of dosing in renal and hepatic impairment. Formatting in new NCCP Regimen Template	Prof Macon Keane
4	16/03/2018	Treatment table updated for standardisation and inclusion of other treatment options.	Prof Macon Keane
5	16/05/2019	Emetogenic potential updated.	Prof Macon Keane
6	21/07/2021	Reviewed. Updated exclusions (hypersensitivity). Amended Dose modifications for adverse events (Table 2). Amended adverse effects (cardiac toxicity).	Prof Macconn Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.