Trastuzumab (IV) Monotherapy - 21 days

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 positive metastatic breast cancer (MBC)</td>
<td>C50</td>
<td>00200a</td>
<td>Hospital</td>
</tr>
<tr>
<td>HER2 positive early breast cancer (EBC)</td>
<td>C50</td>
<td>00200b</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process

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.

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.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trastuzumab</td>
<td>8mg/kg</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride over 90min</td>
<td>1</td>
</tr>
</tbody>
</table>

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<th>Day</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trastuzumab</td>
<td>6mg/kg</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride over 30min</td>
<td>2 and further cycles</td>
</tr>
</tbody>
</table>

*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.

*Trastuzumab is incompatible with glucose solution

*Trastuzumab can be substituted with the subcutaneous formulation where this has been approved locally.
Trastuzumab is administered subcutaneously at a dose of 600mg over 2-5 minutes. 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.

The information contained in this document is a statement of consensus of NCCP and ISMO professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens
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 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 prescribing clinician.
Renal and Hepatic Impairment:

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

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary</td>
</tr>
</tbody>
</table>

Management of adverse events:

Table 2: Dose modification schedule based on adverse events

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

*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.
  
  - 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. 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:


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...
NCCP Chemotherapy Regimen


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>10/2/2014</td>
<td></td>
<td>Prof Macon Keane</td>
</tr>
<tr>
<td>2</td>
<td>30/06/2015</td>
<td>Clarification of LVEF requirement in EBC</td>
<td>Prof Macon Keane</td>
</tr>
<tr>
<td>3</td>
<td>30/5/2017</td>
<td>Clarification of dosing in renal and hepatic impairment. Formatting in new NCCP Regimen Template</td>
<td>Prof Macon Keane</td>
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<tr>
<td>4</td>
<td>16/03/2018</td>
<td>Treatment table updated for standardisation and inclusion of other treatment options.</td>
<td>Prof Macon Keane</td>
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<tr>
<td>5</td>
<td>16/05/2019</td>
<td>Emetogenic potential updated.</td>
<td>Prof Macon Keane</td>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System

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

Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinf/medonc/cdmp/