Trastuzumab 5-Fluorouracil and CISplatin Therapy - 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease	C16	00502a	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 is administered every **3 weeks** for six cycles or until disease progression or unacceptable toxicity develops.

- CISplatin is administered on Day 1
- 5-fluorouracil 800 mg/m^2 per day is given by continuous intravenous infusion on days 1–5 of each cycle.
- Trastuzumab is given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks from cycles 2 onwards.

Facilities to treat anaphylaxis MUST be present when chemotherapy is administered

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Trastuzumab[a]	8mg/kg	IV infusion Observe post infusion[b]	250ml 0.9% NaCl over 90min	1
1	1	Trastuzumab[a]	6mg/kg	IV infusion Observe post infusion[b]	If no adverse reactions use 250ml 0.9% NaCl over 30min	Every 21 days from cycle 2 onwards
2	1	CISplatin[c]	80mg/m^2	IV Infusion	1000ml NaCl 0.9% over 2 hours	Every 21 days for 6 cycles
3	1-5	5-Fluorouracil[d]	800mg/m^2/day (total dose = 4000mg/m^2 over 120 hours)	Continuous IV infusion over 5 days	Infusor pump	Every 21 days for 6 cycles

[a]Trastuzumab is incompatible with glucose solution

[b]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.

[c]**Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
1. Administer 10mmol magnesium sulphate ($MgSO_4$) (+/-KCl 20mmol/L if indicated) in 1000mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (3, 4).

[d]See dose modifications section for patients with identified partial DPD deficiency

ELIGIBILITY:

- Indications as above
- HER2 overexpression as determined by an accurate and validated assay
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to trastuzumab, CISplatin, 5-Fluorouracil or any of the excipients
- Baseline LVEF < 50% for trastuzumab therapy.
- 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.
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- Known complete DPD deficiency
- Pregnancy
- Lactation

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)
- Audiology and creatinine clearance if clinically indicated
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile prior to each cycle
- LVEF every 12 weeks or as clinically indicated
- Ototoxicity and sensory neural damage prior to each cycle

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:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
    - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Any dose modification should be discussed with a Consultant

Haematological:

Table 1: Dose modification of CISplatin and 5-Fluorouracil for Haematological Toxicity

ANC (x 10^9/L		Platelets (x 10^9/L	Dose
≥ 1.5	and	≥ 100	100%
1 to < 1.5	or	75 to <100	**Delay**[a] then 100% for 1st event[b]
<1	or	<75	**Delay**[a] then 75%
[a]Delay until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L [b]Consider dose reduction to 75% for subsequent events and/ or prolonged delays of more than 2 weeks			

Trastuzumab

- 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 2: Recommended dose modifications in patients with renal or hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td rowspan="5">CISplatin</td><td>GFR (ml/min)</td><td>Dose</td><td colspan="4" rowspan="5">No dose reduction necessary</td></tr>
<tr><td>≥60</td><td>100%</td></tr>
<tr><td>45-59</td><td>75%</td></tr>
<tr><td><45</td><td>Consider CARBOplatin</td></tr>
<tr><td></td><td></td></tr>
<tr><td rowspan="4">5-Fluorouracil</td><td colspan="2" rowspan="4">Consider dose reduction in severe renal impairment only</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>Contraindicated</td></tr>
<tr><td colspan="4">Clinical decision.
Moderate hepatic impairment; reduce initial dose by 33%.
Severe hepatic impairment, reduce initial dose by 50%.</td></tr>
<tr><td>Trastuzumab</td><td colspan="2">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 colspan="4">No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.</td></tr>
</table>

Management of adverse events:

Table 3: Dose modification schedule based on adverse events

Adverse Event	Dose Modification
Stomatitis or Diarrhoea Grade 2 Grade ≥3	 Reduce dose of 5-fluorouracil to 75% Discontinue or delay until toxicity resolved then resume at 50%.
Hand-foot syndrome Grade 2 Grade 3	Reduce dose of 5-fluorouracil to 75% until resolved then consider increasing dose by 100% Delay until resolved then resume at 75%
Neurotoxicity Grade ≥ 2	 Omit CISplatin
LVEF drops 10 ejection fraction points from baseline and to below 50%	Withhold treatment with trastuzumab. Repeat LVEF after 3 weeks. No improvement or further decline-consider discontinuation. Discuss with consultant and refer to cardiologist.
NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue trastuzumab
Haematological	See Table 1 above for CISplatin and 5- fluorouracil. Treatment with trastuzumab may continue during periods of reversible, chemotherapy-induced myelosuppression. Monitor carefully for any complications of neutropenia.
Symptomatic heart failure	Discontinue trastuzumab

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Trastuzuamb: Minimal **(Refer to local policy).**

CISplatin: High **(Refer to local policy).**

5-fluorouracil: 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:

Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above).**
Anti-diarrhoeal treatment **(Refer to local policy).**
Mouth care **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

- **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.
- **Myocardial ischaemia and angina**: Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil
- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle of CISplatin

DRUG INTERACTIONS:

- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary, monitor renal function closely
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydroprimidine dehydrogenase activity.
- A possible interaction with warfarin and trastuzumab 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 (5).
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CISplatin	L01XA01
5-Fluorouracil	L01BC02
Trastuzumab	L01XC03

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Version	Date	Amendment	Approved By
1	13/08/2018		Prof Maccon Keane
2	30/07/2020	Updated exclusion criteria Updated baseline tests Updated emetogenic potential Updated adverse events	Prof Maccon Keane
3	26/8/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.