CISplatin and Capecitabine Adjuvant Chemoradiation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
Adjuvant treatment of adult patients with resected gastric cancer stage IIA or higher and no distant metastases	C16	00473a	CISplatin: N/A Capecitabine: CDS

*This applies to post 2012 indications only

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.

Chemotherapy is given in 5 cycles as described in Table 1 below:

- Cycles 1 and 2 - prior to radiation treatment (21 day cycles),
- Cycle 3 - radiation treatment (5 weeks) and
- Cycles 4 and 5 - following radiation treatment (21 day cycles).

Cycle 4 to start 2-4 weeks after completion of radiation.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
CYCLE 1 and 2					
1	[a]CISplatin	60mg/m^2	IV Infusion	1000mL NaCl 0.9% over 2 hours	Every 21 days for 2 cycles
1-14	[b,c,e]Capecitabine	1000mg/m^2 twice daily	PO	n/a	Every 21 days for 2 cycles
CYCLE 3					
1-5	[b,d,e]Capecitabine	825mg/m^2 twice daily on each radiotherapy day only	PO		Day 1-5 week 1, 2, 3, 4, 5 concurrently with radiation.
CYCLE 4 and 5					
1	[a]CISplatin	60mg/m^2	IV Infusion	1000mL NaCl 0.9% over 2 hours	Every 21 days for 2 cycles
1-14	[b,c,e]Capecitabine	1000mg/m^2 twice daily	PO		Every 21 days for 2 cycles

[a] **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 10-20mmol/L if indicated) in 1000 mL 0.9% NaCl over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000mL 0.9% NaCl over 60 minutes
Mannitol 10% may be used 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.

[b]The dose to be administered should consider the available tablet strengths.
Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine- Available on the NCCP website .

Tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. Tablets should not be crushed or cut. [c]**(Total daily dose = 2000mg/m²)** [d]**(Total daily dose = 1650mg/m²)**
[e]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate hepatic, renal, and bone marrow function

EXCLUSIONS:

- Hypersensitivity to CISplatin, capecitabine or any of the excipients
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- Known complete DPD deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy
- Breast Feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiology and creatinine clearance if clinically indicated
- INR tests if patient is on warfarin as clinically indicated
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested
    - In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, renal and liver profile prior to each cycle
- INR tests if patient is on warfarin as clinically indicated

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 2: Dose modifications in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
<1.5	**or**	<75	Delay chemotherapy for 1 week

After 1 week of delay:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1.5	**and**	≥75	100%
1 to <1.5	**and**	≥75	Reduce dose of capecitabine only by 25%
<1	**or**	<75	Delay for an additional week

After 2nd week of delay:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥ 1	**and**	≥75	Reduce dose of capecitabine only by 25%
<1	**or**	<75	Delay for an additional week

After 3rd week of delay:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1	**and**	≥75	Reduce dose of capecitabine only by 50%
<1	**or**	<75	Omit further chemotherapy

Renal and Hepatic Impairment:

Table 3: Dose modifications of CISplatin and capecitabine in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th>Hepatic Impairment</th></tr>
<tr><td rowspan="4">CISplatin</td><td>CrCl (mL/min)</td><td>Dose</td><td rowspan="4">No dose modifications for hepatic impairment</td></tr>
<tr><td>≥60</td><td>100%</td></tr>
<tr><td>45-59</td><td>75%</td></tr>
<tr><td><45</td><td>Hold CISplatin or delay with additional IV fluids or go to CARBOplatin</td></tr>
<tr><td rowspan="2">Capecitabine</td><td>≥30</td><td>100% dose</td><td rowspan="2">*In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis.</td></tr>
<tr><td><30</td><td>Discontinue treatment</td></tr>
<tr><td colspan="4">*Reference Table 5 for dose modification of capecitabine in treatment related hepatotoxicity</td></tr>
</table>

Management of adverse events:

Table 4: Dose Modification for Adverse Events

Adverse reactions	Recommended dose modification
Nausea grade ≥ 3	Reduce dose of CISplatin by 25%
Non haematological toxicity Grade ≥ 2	Delay chemotherapy until symptoms resolved to Grade 1 or less
Hand–foot syndrome Grade 2 Grade 3	 Reduce dose of capecitabine by 25% Reduce dose of capecitabine by 50%

Capecitabine Toxicity

Treatment related hepatotoxicity

Table 5: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		AST, ALT	Dose modification
> 3.0 x ULN	**OR**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

Refer to NCCP regimen 00216 Capecitabine Monotherapy for detailed information on management of capecitabine related adverse events

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin: High **(Refer to local policy)**
Capecitabine: Minimal to low **(Refer to local policy)**

PREMEDICATIONS:

Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above).**

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.

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

CISplatin

- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.

Capecitabine

- **Diarrhoea and dehydration:** This may be dose limiting. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated.
- **Cardiotoxicity:** Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease.

- **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)**: HFS, also known as palmar-plantar erythrodysaesthesia (PPE), is a common side effect associated with capecitabine (see Table 4 for dose modification of capecitabine for HFS).

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.
- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing its toxicity. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Lee J, Lim D, Kim S et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: The ARTIST Trial. J Clin Oncol 2012;30:268-273.
2. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
3. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017 https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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
7. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020 Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0

8. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Accessed July 2020. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-199-001_24102022175647.pdf
9. Capecitabine (Xeloda®) Summary of Product Characteristics. Accessed July 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	13/08/2018		Prof Maccon Keane
2	20/03/2020	Updated recommended dose modifications for capecitabine in renal impairment	Prof Maccon Keane
3	15/07/2020	Regimen review Updated emetogenic potential	Prof Maccon Keane
4	02/09/2020	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
5	18/01/2023	Amended Cisplatin prehydration.	Prof Maccon Keane
5a	03/03/2025	Additional wording added to baseline tests section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.